MODERN MEDICAL MONOGRAPHS

Edited by

HUGH MACLEAN, M.D., D.Sc., F.R.C.P.

Professor of Medicine, University of London

MODERN METHODS IN THE DIAGNOSIS AND TREATMENT OF GLYCOSURIA AND DIABETES

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BY

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PREFACE TO FOURTH EDITION

THE present edition contains some additional material particularly relating to the value of insulin in diabetes. Our experience of insulin has now been sufficient to enable us to give a more or less definite pronouncement as to its position in diabetic therapy. Briefly, it can be said with a large measure of assurance that insulin, when properly used, is capable of restoring to comparative health and comfort all patients who are suffering from diabetes, provided no other complications are present. Its value in cases of glycosuria in elderly patients may not always be so marked, but this is generally dependent on the presence of degenerative changes of various kinds along with the glycosuria. Contra-indications to the use of insulin are discussed in the text, but they may be summed up as *angina pectoris* and *cardiac degenerations*. Insulin, when administered according to the directions given here, is quite safe, and never produces any unpleasant symptoms. Such a wonderful therapeutic agent in the treatment of diabetes should be much more extensively employed by medical practitioners.

H. MACLEAN.

LONDON,
August, 1927.

PREFACE TO FIRST EDITION

THE present monograph follows the same lines as my small volume on Renal Disease. It aims at giving to the busy general practitioner a short and concise account of our present knowledge of diabetes and glycosuria in so far as this knowledge bears on the clinical aspect of these conditions. A good deal of space has been devoted to the changes in blood-sugar concentration resulting from the ingestion of carbohydrate in the normal individual. This aspect of the subject is an important one, for no true idea of the mechanism by which glycosuria is produced can ever be obtained unless the main facts of normal blood-sugar variations are grasped.

The estimation of blood-sugar is now a simple process and can be successfully undertaken by any medical man with the minimum of chemical equipment. Blood-sugar estimations, carried out in connection with the ingestion of some carbohydrate, provide more information in glycosuric and diabetic cases than any other method, and it is certain that the future will see a great extension of this means of investigation.

A word as to the results of the modern method of dietetic treatment of diabetes, for which we are so largely indebted to Allen, is perhaps necessary here. In my experience the treatment has, in general, entirely failed to fulfil the hopes with which it was originally launched, and many of the claims made on its behalf are not justified by the results. The ease with which sugar disappears from the urine during the early stages of treatment frequently conveys the impression, and encourages the hope, that the patient has undergone a cure. The malady, however, again reappears sooner or later in the majority of cases, and frequently the only result of treatment is a postponement of the usual fatal issue. Often, there seems to be a promise of much to begin with, but, as in the case of the weird sisters, it only requires a little time to "break it to our hope." In a few cases the modern treatment gives wonderful results, and no doubt saves the lives of some patients.

In spite of the above remarks, modern dietetic treatment is the best and only useful method we at present possess

for combating diabetes, and the method should be adopted in all suitable cases. A detailed account of the procedure employed will be found in this volume, but great latitude is permissible, and each medical man can make such changes as seem necessary to him, so long as general principles are observed. Certain suggestions for feeding diabetic patients almost exclusively on fat, milk and other substances have been published in America, but at present their value is obscure, and for this reason they are not described here.

H. MACLEAN.

LONDON,
July, 1922.

PREFACE TO SECOND EDITION

THE exhaustion of the first edition of this work in a few months appears to justify the view that it was found to be of some service to the medical practitioner. Since the first edition was published the whole problem of diabetic treatment has been entirely changed by the advent of insulin, and the present volume contains full details as to the use of this remedy. I should like to take this opportunity to impress upon medical men the urgent necessity for making themselves familiar with the general principles involved in the use of insulin. When the instructions given here are followed it is almost impossible for any dangerous symptoms to arise, and any medical practitioner can with safety use the remedy if he takes the trouble to master the small amount of knowledge necessary for its administration. Insulin may be a dangerous remedy when used in certain ways, but experience shows that its use on the lines indicated is practically devoid of danger. The fact that patients are still dying from diabetic coma, without any attempt being made to save them by the use of insulin, is a condition of affairs for which there is now really no excuse. Whatever view the general practitioner takes as to the treatment of ordinary diabetes without coma symptoms, it is essential that he should give insulin in all cases of established or threatened coma; indeed, he is under a moral obligation to do so.

H. MACLEAN.

LONDON,
December, 1923.

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CHAPTER I

SOME GENERAL OBSERVATIONS ON DIABETES

Though the literature of the Ancients contains many allusions to a somewhat mysterious disease which was accompanied by polyuria and other diabetic symptoms, it was left to the English physician Thomas Willis, who died in 1675, to make the fundamental, if apparently simple observation that the urine in this disease was sweet. This discovery resulted from the obvious process of tasting the urine, when it was found to be "wonderfully sweet, as if containing honey or sugar." The real cause of this sweetness, however, he failed to recognise, and it was not until about a hundred years later that the true significance of Willis's discovery was grasped. In 1776 another English physician, Dobson, carried out various experiments on diabetic urines, and observing that such urines underwent alcoholic fermentation, came to the conclusion that the sweetness observed by Willis was due to sugar. In proof of this he evaporated down a large amount of a patient's urine, and succeeded in obtaining a whitish cake which weighed over 4 ounces and behaved, in general, like ordinary sugar. Thus, the presence of sugar in diabetic urine was definitely established, though the nature of this sugar had not yet been determined.

The presence of other important substances in diabetic urine followed at much later date. In 1857 Peters discovered that acetone was frequently excreted in

diabetes, and in 1884 oxybutyric acid was found by two independent observers—Kulz and Minkowski.

These important observations laid the foundation for the various elaborate investigations on diabetes which now make the reading of the literature such a herculean task. Though contributions continue to appear in almost alarming numbers and bulk, nothing very material as to the cause of the disease is known, and diabetes still continues to present many unexplained features which are at once the fascination and despair of the clinician and the chemist alike. From the biochemical point of view, the disease is a baffling mystery. At first sight it may appear strange that so little light has been thrown on this malady by the great advances of modern chemistry, but when we consider that such a comparatively simple process as the formation of alcohol from sugar by the yeast cell is not yet understood, we can appreciate the enormous difficulties attending the investigation of diabetes. In alcoholic fermentation by yeast, the process can be experimentally controlled in various directions: the temperature may be changed, the effect of different substances on the activity of the fermenting cell can be ascertained, and the yeast cell may even be broken up and the juice so obtained used for fermentation. Such control is obviously impossible in the case of the complex animal organism, yet even in the simpler yeast fermentation we are to-day more or less ignorant of the processes that go on, and the nature of the intermediate bodies produced between the sugar on the one hand and the alcohol and carbonic acid on the other hand is by no means satisfactorily established. If in yeast fermentation of sugar, where various experimental manipulations can be carried out without detriment to the process, we still know so little of the essential mechanism, is it at all a matter of surprise that the nature of sugar metabolism in the body is quite unknown? Indeed, a realisation of the great difficulties encountered in experiments conducted *in vitro* suggests

that a knowledge of sugar metabolism in animals will for long prove a difficult and laborious problem. Such knowledge must obviously precede the elucidation of diabetes, but it must be remembered that diabetes is not a disease of carbohydrate metabolism alone, but is associated with marked changes in protein and fat metabolism as well.

Nature of Sugar in Diabetic Urine.

It is now well recognised that the sugar found in diabetic urine is glucose or grape sugar, and though traces of other sugars, such as lævulose, may occasionally be found, they are of rare occurrence and unimportant. Glucose ($C_6H_{12}O_6$) is the particular sugar with which the body deals, and this sugar forms the end product of digestion of the various starchy materials taken as food. Unlike cane sugar and other disaccharides, it ferments with yeast and forms a characteristic compound with phenylhydrazine, which may be used for its identification. From its property of rotating the plane of polarised light to the right, it is sometimes referred to as dextrose. It reduces various metallic oxides in alkaline solution, a property on which all the usual tests for sugar are based. Glucose is derived chiefly from the carbohydrate part of the diet, but it must not be forgotten that a certain amount may arise from protein as well.

Perhaps, however, sugar is not the most important abnormal constituent of diabetic urine, for the so-called "ketone bodies" already mentioned—acetone, diacetic acid, and oxybutyric acid—are always present in severe cases, and frequently give a good general indication of the gravity of the disease and its rate of progress towards a fatal issue. The ketone bodies arise chiefly from the fat of the diet.

The Ketone Bodies in Diabetic Urine.

Of the metabolism of fat in the animal body we know as little as we do of carbohydrate metabolism, but there is a good deal of evidence that, normally, certain of the

end products of fat metabolism consist of the "ketone bodies" found in diabetic urine. Of these, the first product to be considered is oxybutyric acid. The reader will perhaps remember that the series of fatty acids consists of bodies made up of chains containing the group CH_3 at the one end and the group COOH at the other end. The acid with two carbon atoms is represented by the chemical formula $CH_3.COOH$, and is acetic acid. Any higher acid of this series is formed by a corresponding addition of CH_2 radicles. Thus the three-carbon fatty acid is written $CH_3.CH_2.COOH$ (propionic acid), and the four-carbon acid (butyric acid) as $CH_3.CH_2.CH_2.COOH$. For purposes of reference it is customary to refer to the carbon atom in the CH_2 next to the COOH, or carboxyl group, as the α carbon, while the carbon of the adjacent CH_2 group is known as the β carbon. In the fatty acid found in diabetic urine, the H attached to the β carbon is substituted by the (OH) or hydroxyl group, so we get $CH_3.CH(OH).CH_2.COOH$, which is really hydroxybutyric acid, but is generally referred to as oxybutyric acid. By the addition of oxygen to the CH(OH) group of oxybutyric acid one molecule of water is eliminated and a (CO) group left. Oxidation of oxybutyric acid thus results in the formation of a substance with the formula $CH_3.CO.CH_2.COOH$, which is diacetic acid or acetoacetic acid.

Diacetic acid readily gives up carbon dioxide (CO_2) from its COOH group, leaving one H, which is transferred to the adjacent CH_2. This results in the formation of a substance with the formula $CH_3.CO.CH_3$, which is acetone.

It is thus obvious that there is a very close relationship between these three bodies, which are easily formed one from the other. Whether the original substance formed in the body is oxybutyric acid or diacetic acid has been the subject of some controversy; obviously each might be derived from the other. There is no doubt, however, that diacetic acid is the precursor of acetone, and in this con-

nection it is worth noting that a urine which gives certain tests for diacetic acid when freshly passed may, after standing for some time, give no reaction for this substance, the diacetic acid having changed into acetone.

As a working hypothesis, we may for the present assume that, in the body, oxybutyric acid is the first acid formed, and that this acid gives rise to diacetic acid, which in turn yields acetone.

Diabetes a Disease of Varying Grades of Intensity.

Diabetes may be summed up as a wasting disease with various well-recognised symptoms, such as polyuria, thirst and hunger; the glycosuria is often accompanied by the presence of " ketone bodies "—acetone, diacetic and oxybutyric acids—in the urine. The malady in general tends to progress towards fatal coma. This, however, refers to a typical case, but a very small experience of diabetes soon makes it obvious that all shades of severity, from a condition in which the only symptom is the presence of slight glycosuria to one in which the symptoms are so pronounced as to merit the application of " fulminating " diabetes, are met with from time to time. This suggests the question: When a patient is suffering from glycosuria and no other symptoms, should he be regarded in all cases as a diabetic ? This is more fully discussed later (Chapter III.), but it seems quite certain that many glycosurics, even when untreated, never develop the typical picture of diabetes. At present the general trend of opinion is to regard every case of glycosuria as a potential diabetic, but it must be emphasised that glycosuria, especially when of a transient nature, is not of such infrequent occurrence as some observers seem to think, and is frequently of little or no importance. Apart from cases in which sugar appears in the urine as the result of a " leaky " renal system, there is sufficient evidence that several untreated cases of even persistent and fairly well-marked glycosuria never develop into true

diabetes. It is a safe rule to treat every case of glycosuria as diabetes until it is proved not to be so, but certain of the advocates of this wise policy apparently make little or no attempt to exclude diabetes in these doubtful cases. They tend to accept the view that glycosuria is essentially diabetic in nature, and treat all their glycosuric cases as potential diabetics, without making use of the means which are now available to help in discriminating between the different conditions. This method is a safe one, but sometimes inflicts a quite unnecessary amount of bodily and mental anguish on the patient. When it is adopted, the results of treatment, expressed in the form of statistics, are obviously quite impressive, but many of these patients would do equally well without any treatment at all. Granted, it is difficult in many cases to be certain whether the condition is one of diabetes or not, but the use of modern methods helps us in very many instances to say quite definitely what the condition is. All cases of doubtful glycosuria should be investigated on the lines described later, when it will frequently be found that no indications for drastic treatment are present. Indeed, in many cases of mild and persistent glycosuria, some slight abnormality such as a lowered renal threshold will be found to explain the condition. Personally, I know of several practically untreated patients who have been passing sugar for over twenty years, and yet they enjoy quite average health for their ages; some of them, indeed, are exceptionally strong and active, while others, though not so robust, do not appear to be in any way injured by the glycosuria. One case shows certain eye changes, probably due to the hyperglycæmia, but in no instance has the condition passed on to one of ordinary diabetes.

For the sake of the patient it should never be forgotten that glycosuria does not constitute diabetes, and in doubtful cases every effort should be made to ascertain the true nature of the process. Glycosuria should never be taken lightly, but, on the other hand, it should not be looked upon as a necessarily serious condition, and all

the methods now at our disposal should be used to determine the cause. When the physical mechanism on which glycosuria depends is once thoroughly grasped, it will be found quite easy to understand why the condition exists in certain patients. Generally speaking, examination of the urine teaches us but little as to the cause of glycosuria, but examination of the blood-sugar is frequently of very great importance. The extreme ease with which the blood-sugar can now be estimated leaves little or no excuse for neglecting this important procedure, but before conclusions can be drawn the normal changes in blood-sugar concentration must be appreciated. To a great extent, ordinary glycosuria is dependent on the physiological changes of blood-sugar concentration following the intake of carbohydrate diet. This is fully discussed in Chapter III.

Even in patients showing symptoms of undoubted diabetes there is a tremendous variety in the progress of the different cases. Some patients, even when practically untreated, do not seem to get much worse—at least, for many years; others proceed rapidly to a fatal termination in spite of the most careful dieting and general hygiene. Between these extremes there are all degrees of severity, and this fact should be remembered in estimating the effect of modern treatment on diabetes.

Views as to the Cause of Diabetes.

On looking through the older literature of diabetes one is impressed by the frequent references of observers to definite pancreatic lesions found at necropsies on patients dying from this disease.

The epoch-making paper of Von Mering and Minkowski, published in 1889, focussed attention on this organ, for these investigators showed that the removal of the pancreas from an animal resulted in a condition which was practically the same as severe human diabetes. Removal of part of the gland might or might not produce glyco-

suria, according to the amount of healthy tissue left behind, but complete extirpation was followed, in every case, by intense symptoms and a fatal termination within a few weeks. These classical experiments proved beyond doubt that the pancreas is necessary for carbohydrate metabolism, and that disease of the pancreas would result in diabetes. Evidence was obtained that these phenomena were not dependent on the loss of the ordinary pancreatic acini, and it is now generally held that certain small islands of special cells found in the pancreas—the islets of Langerhans—are responsible for the production of an internal secretion which is essential for normal carbohydrate and general metabolism. The destruction of these islands results in diabetes.

Following these experiments, the tendency to ascribe all cases of human diabetes to defects in the pancreatic islands was naturally very great, but it must be admitted that histological evidence, so far, does not bear out this contention. Everyone who has conducted many diabetic necropsies must have been struck by the fact that in a very large number of cases the pancreas is apparently quite normal. This macroscopic examination is, of course, no proof that the pancreatic islets are healthy, but frequently a careful microscopic investigation fails to reveal any histological changes. Some cases undoubtedly present marked features of degeneration of the islets, and one can at once accept this as definite evidence of pancreatic inefficiency, but in many fatal cases of diabetes the islets appear to be quite as healthy as in normal individuals. In America much interesting work on this point has recently been carried out, especially by Allen and his colleagues, who have published extensive papers on the subject in the *Journal of Metabolic Research.*

The presence of different kinds of cells in the pancreatic islands was definitely established by Lane in 1907. Lane used special staining methods, and by this means was able to differentiate what he designated as alpha and beta cells. Later, the very interesting observation

was made that, in experimental diabetes, only the beta cells underwent degeneration, while the alpha cells persisted in their original form. Following up these results, Allen found that the degeneration of the beta cells in experimental animals from which part of the pancreas had been removed, was governed by the intensity of the diabetes, which in turn, of course, was dependent on the size of the pancreas remnant left behind and the diet. Allen's latest views are that the hydropic degeneration of the islets of Langerhans, found in experimental diabetes, is produced solely by overstrain of the function of the cells by diets in excess of the weakened assimilative power. This is an important observation, since it explains the permanent lowering of assimilation in diabetics following excessive diets, and affords proof that progressive degeneration of the essential pancreatic tissue, and consequent increase in symptoms, can be produced by injudicious dietetic treatment of our patients. Some evidence was also obtained that recovery from this degeneration might take place by the use of proper diet, provided the process had not become too extreme.

The loss of the beta cells is, however, not the only important feature in diabetes, for certain well-marked differences are observed to exist between totally depancreatised dogs and dogs with extensive partial pancreatectomy. In both cases the diabetes is hopeless, but in the partially depancreatised animal with complete degeneration of the beta cells the asthenia is generally much less, and wounds heal almost as well as in the normal dog; the duration of life is generally longer, and such a dog, if fed on fat, may retain a well-nourished and sleek appearance and die in coma without emaciation. According to Allen, these differences indicate that the very marked cachexia of the totally depancreatised animal is not due solely to the lack of power to assimilate carbohydrate, and that the small part of the pancreas remaining in the partially depancreatised animal must play some part in metabolism; consequently, the pancreas must

furnish an unknown secretion other than that from the beta cells, which is not directly concerned in sugar metabolism, but is in some way necessary for the animal welfare. Though the metabolism of sugar is intimately connected with the beta cells, the production of acidosis and coma may occur in certain animals, and yet the subsequent examination of the pancreas may show quite normal unchanged beta cells. This is particularly well seen in many cases of human diabetes.

If we take the view that the pancreas is primarily at fault in all cases of human diabetes, it is necessary to assume, in cases in which the essential pancreatic cells are apparently normal from the histological point of view, that these cells are defective in function. In other words, that the change is a so-called functional one. This is an unsatisfactory position, and though the experimental evidence is all in favour of a pancreatic lesion as the cause of diabetes, it is quite possible that certain cases are not pancreatic in origin. After all, the pancreas constitutes but one of the known links in an unknown chain, and it may well be that other parts of this chain, which cannot be experimentally investigated, may be the seat of defective action in some instances of human diabetes. That the liver plays an important part in diabetes is certain, and while this is generally a secondary phenomenon, there is no proof that the primary defect may not occasionally reside in the liver or other organ. The connection of the islets of Langerhans with carbohydrate metabolism has been amply established, but the lack of definite evidence of pancreatic involvement in a large number of diabetic necropsies is so unlike our usual experience in other pathological conditions that we cannot, with complete satisfaction, assume that the pancreas is necessarily the site of the lesion in all diabetic patients. Possibly, the future may establish the presence of definite pancreatic inefficiency as the cause of all diabetes but at present we can but surmise, and no amount of emphatic declaration on the part of the advocates of this

theory can alter the fact that, in many cases of human diabetes, the only evidence of pancreatic inefficiency is purely inferential. So far, the advent of insulin has done little to clear up the difficulty.

The Effect of Food in Diabetes.

One of the most striking phenomena associated with diabetes is the presence of sugar in the urine, and this glycosuria has tended to concentrate attention almost exclusively on the defect in carbohydrate metabolism present in this disease. Indeed, diabetes is sometimes referred to as a condition in which the specific defect is an inability of the body to deal with starchy food, and no notice is taken of the fact that defects in fat and protein metabolism may play an equally large part in the malady. Diabetes is a disease of metabolism in which all the food-stuffs are implicated to a large extent. The sugar in diabetic urine is chiefly derived from starch taken as food, but protein can also produce sugar, and in bad cases a large amount of the sugar may arise from protein. It has been shown that, of the twenty or so amino-acids resulting from protein hydrolysis, about half of them produce glycosuria when given to a suitably prepared animal, while the remainder produce no glycosuria, but give rise to acetone and diacetic acid bodies instead. No doubt, this is the ordinary mechanism, but in health there is no evidence of the production of these intermediate products, since they are quickly changed and never allowed to accumulate in the body. In severe diabetes, it is common enough to come across patients who pass large amounts of sugar when on carbohydrate-free protein diet; it is also frequently observed that increase in the protein of the food results in increased production of acetone and diacetic acid. Fat does not give rise to sugar directly, but indirectly it may cause the appearance of sugar in diabetes, especially when large amounts are taken. Fat is the most important source of the acetone bodies, for an increase of fat in the diabetic

diet will frequently give rise to large amounts of these ketone bodies in the urine; when the fat is reduced, the ketonuria gets less or may disappear altogether. These observations are of great importance in connection with the intelligent treatment of diabetic patients. Frequently it is easy enough to get rid of glycosuria by giving large amounts of fat with protein instead of carbohydrate, but here the resulting acidosis may be much worse than the glycosuria. Often, by a judicious balancing of the diet, it is possible to give the necessary nourishment to the patient, and yet maintain a condition in which the urine is both sugar and acetone free, and this is really what we aim at in the treatment of diabetes. In severe cases the withdrawal of carbohydrate and its replacement by fat simply gets rid of one difficulty to produce another one. The glycosuria may disappear, but the acetone and diacetic acid in the urine may become dangerously abundant. A glance at Fig. 1 will make clear the relation of the different foodstuffs to the glycosuria and ketonuria of diabetes. It is assumed that carbohydrates, on the one hand, and fats on the other, have each a definite specific path of metabolism. In the case of carbohydrate, all starchy food taken in is broken up in the intestine and absorbed as sugar, which passes by way of the portal vein to the liver, where it is largely stored as glycogen. When sugar is required by the muscles and other tissues this glycogen is broken down, and the resulting glucose transported to the tissues, where it is oxidised. The ultimate results of normal glucose metabolism are carbon dioxide and water, but we know little with certainty of the intermediate products. In diabetes a large part of this sugar, instead of being used in the body, is thrown out in the urine.

Normal fat metabolism probably results in the formation of such intermediate substances as oxybutyric acid, diacetic acid, and acetone, which are ultimately oxidised to carbon dioxide and water, just as in the case of sugar. In diabetes this final oxidation is difficult to accomplish,

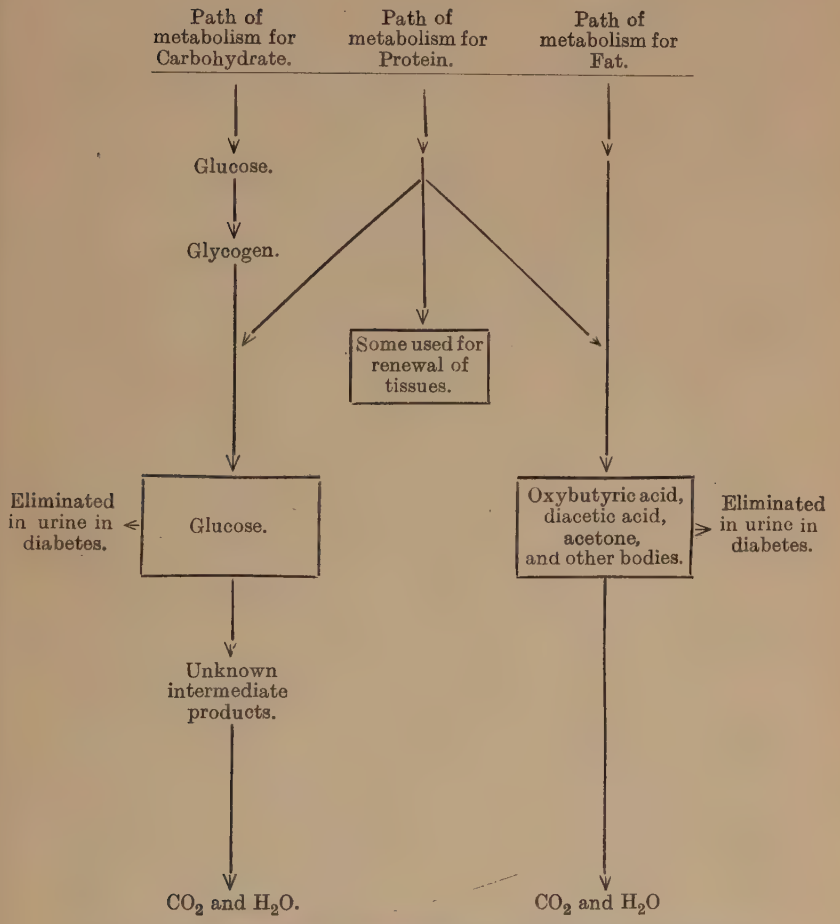

FIG. 1.—DIAGRAMMATIC REPRESENTATION OF METABOLISM OF DIFFERENT FOODSTUFFS, SHOWING RESULTS OF PROTEIN FEEDING IN DIABETES.

so that these ketone bodies accumulate in the blood and are excreted in the urine. The glycerine of fat may also form a little sugar in the body.

Protein may be looked upon as having no specific metabolic path for the supply of energy, for when it furnishes the necessary nitrogenous material lost by the wear and tear of the body, it supplies energy to the body either by way of the carbohydrate or the fat metabolic path. Protein circulates in the blood as amino-acids produced by hydrolysis in the intestine, and these different acids are picked up by the various tissues according to their needs. When the nitrogenous waste of the tissues is supplied, the remaining acids undergo a process whereby the nitrogen is removed; this nitrogen is eliminated from the body as urea. The nitrogen-free amino-acid moiety now joins either the carbohydrate or the fat path, according to the nature of the particular deamidised amino-acids present. Protein may therefore be looked upon as a combination of nitrogen-replacing material which, in the body, supplies to some extent the place of both fat and glucose. These points are represented diagrammatically in Fig. 1, which shows in simple form the effects of the different foodstuffs in diabetes.

It cannot be too strongly emphasised that diabetes is a disease of general metabolism in which all the ordinary foodstuffs are involved. No real knowledge of the principles underlying the modern treatment of the disease can be obtained unless this point is appreciated, for it is chiefly on the recognition of this principle that modern diabetic treatment is founded. In the long history of diabetic therapy, this essential fact, though sometimes suggesting itself in a dim and indistinct manner to certain observers, was thoroughly grasped only in quite recent times. It is safe to say that the better results now obtained in the treatment of this condition are due to a better understanding of the broader basis of the malady. Various practical points bearing on the diagnosis and treatment of diabetes are discussed under appropriate headings in the following chapters.

CHAPTER II

BLOOD-SUGAR IN HEALTH AND IN DIABETES

Improved methods of blood-sugar estimation introduced during the last few years have materially increased our knowledge of the changes which the blood-sugar undergoes both in health and in diabetes. These changes result chiefly from the taking of carbohydrate food, and are very marked both in the normal and in the diabetic individual. In dealing with patients suffering from glycosuria of any kind, it is essential that the differences in concentration which the blood-sugar undergoes in the normal subject should be clearly recognised, otherwise it is impossible to understand the mechanism on which glycosuria depends. A very simple method for the estimation of blood-sugar is described in detail on p. 59, so that there is no longer any reason why this simple and essential procedure should be neglected. In my experience, much more information as to the underlying condition can be obtained from blood-sugar estimations on glycosuric patients than by any other method of investigation, and it would seem as if the value of this procedure has hardly as yet been appreciated. In order to arrive at correct conclusions in any given case, various points must be taken into consideration; these points are fully discussed in the following pages.

Normal Blood-Sugar.

In the normal healthy individual the blood-sugar varies from time to time, but when estimated a few hours after food it should, generally speaking, lie between 0·09 and 0·11 per cent. Under certain circumstances it may be a little higher or a little lower than this, but the round

figure of 0·1 per cent. is generally accepted as the normal for average individuals. Formerly, there used to be an idea that the blood-sugar concentration was practically constant, and never varied to any appreciable extent; but we know now that this is an erroneous view, and that the amount of sugar in the blood is constantly changing from hour to hour. This is very well brought out when the blood-sugar is estimated at intervals after the ingestion of sugar or starchy foods.

The Effect of Sugar Ingestion on Blood-Sugar Concentration in the Normal Subject.

In estimating the changes in blood-sugar concentration caused by the ingestion of sugar it is best to ascertain the blood-sugar content immediately before giving a dose of, say, 50 grams of glucose. Samples of blood are then taken at frequent intervals, when marked changes in the blood-sugar concentration will be found. In the average young or middle-aged healthy individual, the concentration usually rises from the basal figure of about 0·1 per cent. to a maximum of 0·16 or 0·17 per cent., this maximum being obtained in from 30 to 60 minutes or so after the ingestion of the glucose. Naturally, this rise may occasionally be somewhat delayed, so that its highest point may not be reached until after 1 hour, but, as a general rule, the maximum concentration is obtained in from 30 to 60 minutes, and most frequently perhaps in about 30 to 40 minutes. Variations may, no doubt, be dependent on absorption and other factors, but, speaking generally, the highest concentration of blood-sugar should be obtained some time within an hour after sugar is taken. The maximum concentration found varies somewhat, and in some patients the blood-sugar does not apparently exceed about 0·15 per cent., while in others it may reach 0·18 per cent. Obviously, the exact amount found will depend on the particular time at which the blood is taken, for this maximum concentration is sustained only for a

short period—perhaps sometimes only for a few minutes —and it is just a chance whether or not we happen to take a sample at this point.

Immediately after the maximum concentration is attained a very curious change takes place. The blood-sugar now gets less and less, until very soon it is lower than it was to begin with. From the maximum point it takes about the same time to fall as it took to rise, so that, in the average individual, no indication of any increase in

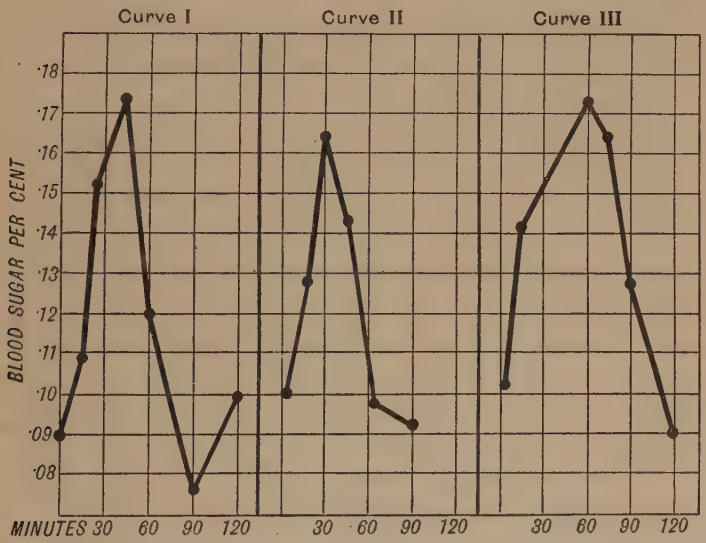

Chart 1.—Showing Effect of 50 Grams Glucose by Mouth on Blood-Sugar Content of Three Different Subjects.

blood-sugar can usually be found in about 1½ hours after the sugar has been taken by mouth; indeed, a sample of blood taken after this time frequently shows a lower blood-sugar concentration than was present to begin with. These points are well brought out in the curves shown in Chart 1. In each case 50 grams of glucose dissolved in 150 c.c. water were given. The subjects were all healthy individuals between twenty-five and forty years of age, and the tests were carried out from 3 to 4 hours after the last meal, which contained very little carbo-

hydrate. In Curve I. the blood-sugar reached its maximum in about 45 minutes; after 80 minutes it was back again to about 0·1 per cent., and in 90 minutes reached the low level of 0·077 per cent., from which it quickly swung back to about 0·1 per cent. within the next 30 minutes.

In Curve II. the maximum blood-sugar concentration (0·165 per cent.) was obtained after 30 minutes, while in 1 hour it was again down to its original level of 0·1 per cent.

In Curve III. the maximum concentration was delayed for about 60 minutes, when a blood-sugar content of 0·172 per cent. was found. In 90 minutes this had decreased to 0·128 per cent., and in 120 minutes was 0·09 per cent. In this case all the effects were somewhat delayed, perhaps owing to some interference with absorption.

These results are typical of the effect produced by the ingestion of glucose in the normal individual. In children under three years of age, as shown by Spence,* the rise in blood-sugar is very much less marked, the maximum concentration seldom exceeding 0·12 or 0·13 per cent. when from 7 to 15 grams of sugar are given, an amount which represents much more than 50 grams in the adult. In children over three years of age the blood-sugar curve represents that of a young adult. As age advances there is a tendency for the curve to be prolonged, and in persons over sixty years of age in good average health a blood-sugar concentration amounting to 0·13 or 0·14 per cent. may persist as late as 2 hours after the 50 grams of glucose are taken.

On the Cause of Blood-Sugar Variations after taking Sugar.

The rise in blood-sugar after the ingestion of glucose or other carbohydrate is easily understood; it means simply that a large amount of sugar is being absorbed into

* *Quarterly Journal of Medicine*, 1921, **14**, 314.

the blood-stream. When we try to explain the marked fall that follows shortly after the maximum concentration, the problem is much more difficult. At first sight the obvious explanation would appear to be that the sugar has been all absorbed in from ½ to 1 hour, and that the fall in blood-sugar naturally follows. This, however, is not so, as can be easily shown when we give a dose of glucose to a diabetic patient. In the diabetic, the curve obtained is quite different from that given by the normal individual, and the kind of curve obtained in any given case will frequently provide information of much value.

The Diabetic Curve.

In Chart 2 the curve obtained from a severe case of diabetes after the ingestion of 40 grams of glucose is contrasted with that of a normal after 50 grams. The blood-sugar in the diabetic had been reduced to nearly normal by appropriate treatment. At the end of the first hour the rise in blood-sugar is the same in both cases—70 milligrams per 100 c.c.—but from this point onwards there is no resemblance between the two curves. While in the normal the blood-sugar falls rapidly and in the next 30 minutes has regained its original level, in the diabetic it continues to rise steadily and attains its maximum in 2½ hours. Even at this point there is no tendency to any abrupt fall, but a slow decline, which at the end of 4½ hours still leaves the sugar content of the blood at 0·233 per cent. as contrasted with an original level of 0·130 per cent. A comparison of the two curves immediately suggests an explanation of the shape of the normal curve. It appears almost certain that the check in the rise of the normal's blood-sugar during the second 30 minutes is not due to any falling off of absorption, nor can the abrupt fall in the 30-minute period signify that absorption has come to an end. In the diabetic the blood-sugar is still rising during this time, and absorption is therefore still going on, the amount of sugar taken being adequate to raise the sugar content of the blood by

130 milligrams per 100 c.c. In contrast to this the normal curve, after reaching 0·16 per cent.—a total increase of 64 milligrams per 100 c.c.—shows a rapidly diminishing rate of ascent and then an abrupt drop. The fall in the normal curve cannot therefore be due to the cessation of absorption, and two alternatives only remain—that a rise in the catabolism of sugar suddenly occurs, or that the sugar is removed from the blood and

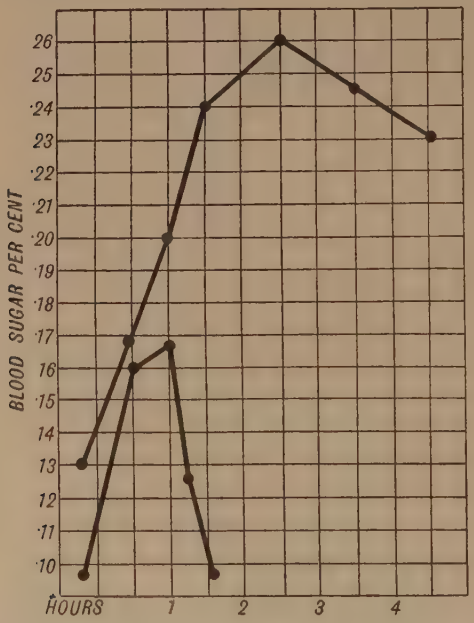

Chart 2.—Showing Diabetic (Upper Curve) as against Normal (Lower Curve).

stored more quickly than it is absorbed. For the first alternative there is no evidence, and such a procedure would obviously be highly wasteful. We must assume, therefore, that the drop in the normal curve is caused by the sudden intervention of a storage mechanism which abstracts the sugar from the blood more quickly than it enters, and, as a result, masks the later stages of absorption. The absence or impairment of such a mechanism

in diabetes makes the curve in the diabetic a much truer picture of the absorption rate than in the normal, though even in the diabetic the result is complicated by a considerable loss of sugar through the kidneys and by any catabolism of sugar that may still be taking place.

From the curves given on p. 17, which show the effect of the absorption of glucose on the blood-sugar content of the normal individual, it appears that the storage mechanism comes into action when the blood-sugar reaches a concentration of about 0·16 per cent. or 0·17 per cent. It is most interesting to note that this is just about the point at which the kidney begins to excrete sugar. Any concentration of blood-sugar above this is indicated by the appearance of sugar in the urine, but the kidney does not begin to excrete sugar until the blood contains something in excess of 0·17 per cent. This " threshold " for sugar, no doubt, varies somewhat in different individuals, and may occasionally be a little higher than the figures given, but the great majority of healthy people tend to have glycosuria whenever the blood-sugar approaches the region of 0·2 per cent. In general, storage of sugar begins at about the level at which active excretion of sugar by the kidneys commences, and hence, in the individual with unimpaired capacity for dealing with carbohydrate and possessing a normal renal threshold, no glycosuria follows the ingestion of even large amounts of carbohydrate. This storage mechanism is so efficient that it is difficult, and frequently impossible, to force the blood-sugar above this level, however large an amount of carbohydrate is ingested. Contrary to general opinion, a dose of 200 to 300 grams of glucose will seldom produce glycosuria in the normal subject, though it may prolong the time during which the blood-sugar curve remains comparatively high. This is seen in Chart 3, where the effect of taking three successive doses of 50 grams of glucose at intervals of 15 minutes is shown. Here the blood-sugar after 150 grams glucose did not rise appreciably higher than it did

after 50 grams, but 2½ hours after ingestion of the last 50 grams the blood-sugar was still a little in excess of its level at the beginning of the experiment.

That storage is still actively continuing after the normal blood-sugar curve has regained its original level is probable from a study of the curve of a severe diabetic. In the latter the rise continues long after the

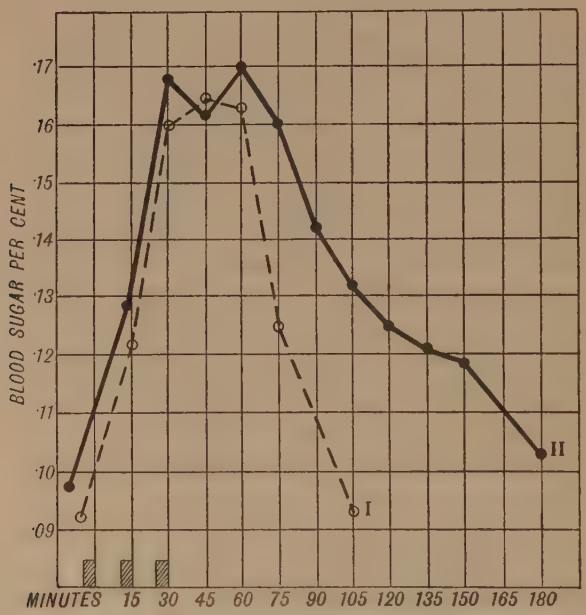

Chart 3.—Curve II. shows Effect of Three Successive Doses of 50 Grams Glucose on Blood-Sugar Content of a Normal Subject. Curve I. shows Effect of 50 Grams Glucose on the Same Subject.

termination of the hyperglycæmia in the normal, indicating that absorption is still in progress. Possibly the hypoglycæmia already referred to, which is often seen at this stage, is an indication of the activity of the mechanism.

In the diabetic this storage mechanism apparently fails in varying degrees, and the extent of its failure can be gauged by the curve obtained after glucose ingestion. As a working rule, if the blood-sugar fails to return to its original level, or nearly so, within 2 hours after a single

50-gram dose of glucose, we may consider that a defect in storage is present. In my experience the healthy individual is well able to deal with such an amount within this time. As already mentioned, a certain allowance must be made in the case of old individuals, for this mechanism is not so active in old age. In all subjects, the quicker the blood-sugar returns to normal the better the storage mechanism.

Nature and Site of Storage Mechanism.

It is probable that the main site of the storage is the liver, for much evidence has been recently obtained that in patients in whom the liver is temporarily involved as the result of toxic poisoning with arseno-benzol and other substances, the storage mechanism for sugar is more or less inefficient. On recovery of the patient the storage power gradually becomes normal. Of course, the muscles must also play some part in abstracting sugar from the blood, but the very marked lowering which suddenly takes place in normal individuals is much more likely to be dependent on a rapid conversion of sugar into glycogen in the liver. It is true that differences between arterial and venous blood in the limbs can be demonstrated, but such differences bear no direct relationship to the height of the blood-sugar, and appear—sometimes, at any rate—to be as marked when the blood-sugar concentration is rising as when it is falling. If the fall in the normal curve were largely due to such storage in the muscles, a direct relationship would be expected. As there is no evidence of this, it is most probable that the storage capacity of the liver is the main factor involved, but direct proof of this can only be obtained by animal experiments.

The Effect of the Ingestion of Varying Amounts of Glucose.

The great sensitiveness of the blood-sugar content to the ingestion of very small amounts of glucose is remarkable. In Chart 4 the curves following the ingestion of different

amounts of glucose are given. It will be seen that such a small amount as 5 grams of glucose gives a slight but quite definite rise in the blood-sugar, while with 10 grams the effect is somewhat increased. The curves were all taken from the same individual, and show that after a certain dose is reached—about 25 grams—further increase in the amount of sugar given does not increase the actual

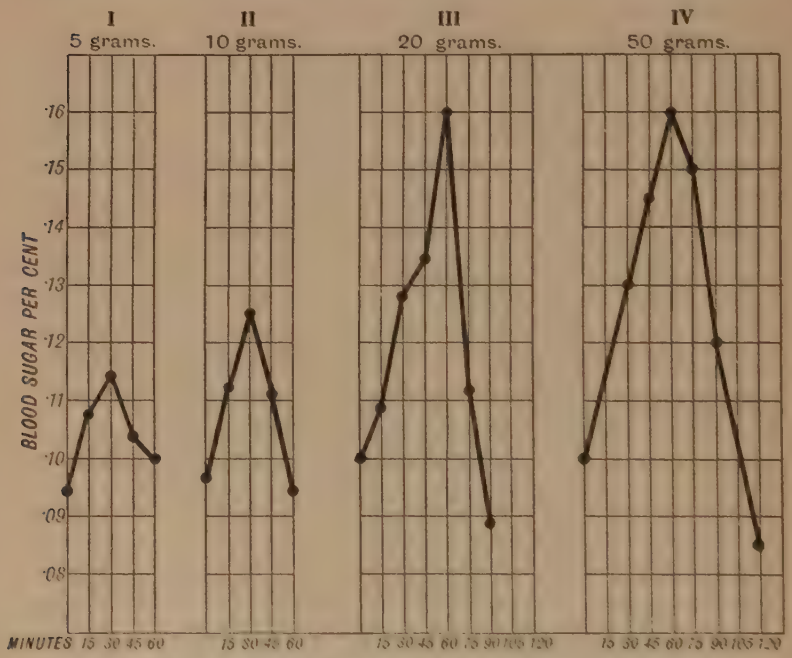

CHART 4.— SHOWING THE EFFECT ON BLOOD-SUGAR OF INGESTION OF DIFFERENT AMOUNTS OF GLUCOSE.

height of the resulting hyperglycæmia. As already mentioned, this increase in the dose tends rather to prolong the period during which the blood-sugar is raised. Even when a second large dose of sugar is given at the top of the curve, this does not raise the blood-sugar concentration. The appreciable rise obtained with 5 grams of glucose is striking evidence of the extreme delicacy of this procedure when used as a test for sugar tolerance.

The Nature of the Curves obtained with Different Sugars.

All the ordinary sugars, with one exception, give definite blood-sugar curves after ingestion. This exception is lævulose, which causes no definite increase of blood-sugar in the normal individual when given in ordinary doses. When, however, the liver is deficient either as the result of a toxic process or of diabetes, lævulose at once gives a curve more or less identical with that obtained with glucose. Lævulose is therefore a very delicate agent for detecting the sugar storage capacity of the liver, and quite recently Brett and Spence* made use of this test in ascertaining liver efficiency in toxic jaundice. Though lævulose does not give any appreciable rise of blood-sugar in the normal individual, it sometimes happens that the urine reduces Fehling's solution after lævulose has been taken. Such urines frequently fail to give the lævulose test, and the explanation of this anomaly appears to depend on the presence of certain impurities in the lævulose which are excreted in the urine, and reduce Fehling's solution. Further evidence of the presence of impurities in certain samples of lævulose is presented by the fact that gastro-intestinal disturbances occasionally follow the ingestion of these samples. In diabetes, lævulose gives practically the same type of curve as glucose.

Of the other sugars, lactose gives a slow and rather prolonged rise, but is obviously easily absorbed by the adult; the nature of its curve suggests that it would tend to cause glycosuria in a susceptible subject to a less extent than the other sugars. The curves obtained from the ingestion of galactose and maltose resemble that of glucose; the same phenomenon is seen as in the glucose curve—a rapid rise to the neighbourhood of 0·17 per cent., followed by a sharp fall. The hyperglycæmia resulting from the ingestion of all carbohydrates appears, in the

* *Lancet*, 1921, ii., 1362.

normal individual, to be limited to about this level—the threshold level for glucose—and cannot easily, if at all, be forced above it. In this fact lies the explanation of the difficulty of provoking glycosuria in the normal individual by giving glucose, a difficulty referred to in several recent publications. Such sugars, as galactose and lactose, however, easily produce glycosuria. For curves obtained with different sugars see Chart 5.

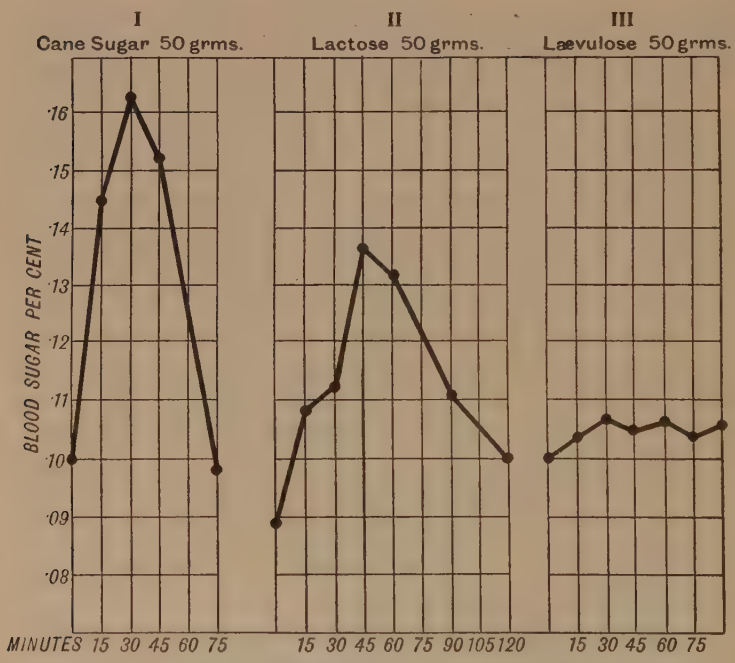

CHART 5.—SHOWING EFFECTS OF DIFFERENT SUGARS ON BLOOD-SUGAR CONCENTRATION.

THE EFFECT OF STARCHY FOODS ON THE BLOOD-SUGAR CONTENT.

The rapid rise in blood-sugar after the ingestion of sugar is easily understood, but it might be thought that any results produced by starchy foods would be much less marked; in particular, we might expect a much slower development of blood-sugar concentration and a lower

maximum concentration than is obtained with such a sugar as glucose. This is, however, by no means the case. The ordinary starchy foods, such as potatoes, rice, corn-flour, and oatmeal, behave almost exactly like glucose when given in proportionate amounts. Chart 6 shows the curves obtained after the ingestion of 100 grams of oatmeal and 250 grams of potatoes respectively. Both results would do very well for normal glucose curves. In

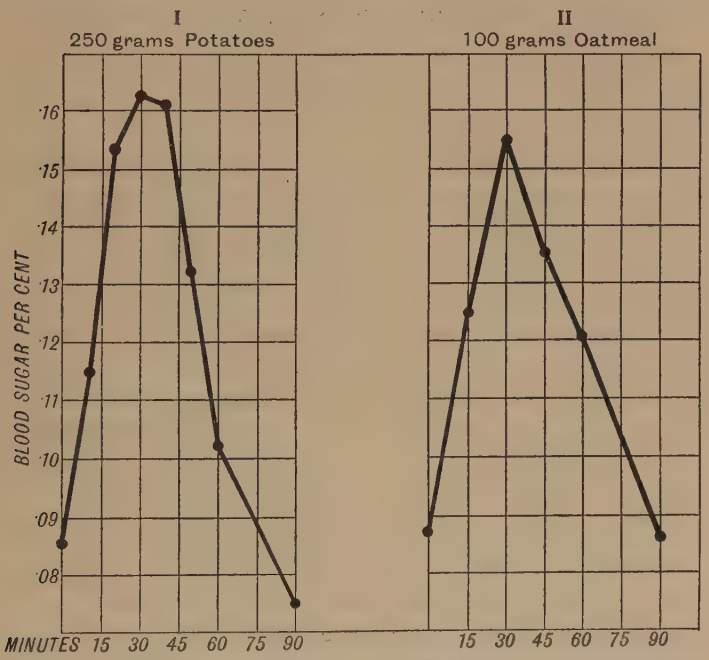

Chart 6.—Showing Effects of Different Carbohydrates on Blood-Sugar.

both cases the blood-sugar reaches a maximum of, roughly, 0·16 per cent., and within 90 minutes returns to a slightly subnormal figure. The extreme rapidity with which these starchy foods are broken up and absorbed is quite striking. It is interesting to note here that the use of oatmeal in diabetes—so warmly advocated by Von Noorden as the "oatmeal cure"—would not seem to be justified, since it behaves, as far as blood-sugar is concerned, exactly like

any other starchy food. The effect of various carbohydrate-containing materials in raising the blood-sugar depends on the readiness with which their carbohydrate can be attacked and hydrolysed in the intestine, so that different vegetable foods containing equivalent amounts of carbohydrate may show quite different effects on blood-sugar concentration.

The Effect of Ordinary Diet on Blood-Sugar Content.

The changes found in the blood-sugar after ordinary mixed meals depend chiefly on the amount of carbohydrate present, but may be influenced to some extent by the other ingredients of the diet. Any effect produced by the non-carbohydrate part of the meal is, however, an indirect one, depending on changes in digestion and absorption in the intestine. There is some evidence, for instance, that potatoes are much more rapidly digested and absorbed when taken alone than when accompanied by large amounts of fat. Diets containing a considerable quantity of easily digested material, such as rice, potatoes, and bread, together with less easily digested material of carbohydrate nature, may show primary and secondary rises in the blood-sugar curve, depending on the relative ease with which sugar is produced in the intestine, but secondary rises are always much lower than the primary ones, and are frequently not seen after ordinary diets, the result obtained being practically the same as that following the ingestion of a corresponding amount of pure carbohydrate.

CHAPTER III

SUGAR TOLERANCE TESTS IN DIABETES AND IN GLYCOSURIA

In the diabetic, as has just been shown, the effect of ingestion of carbohydrate differs materially from that found in the normal individual, and this difference may be utilised as a basis for the investigation of diabetic patients. The most striking phenomenon in the healthy individual is the intervention of a mechanism which prevents the passage of any sugar into the urine even after the ingestion of very large amounts of carbohydrate. Generally speaking, in healthy subjects with normal kidneys, no excretion of sugar takes place until the concentration in the blood reaches about 0·18 per cent. or somewhat more, and it is difficult or impossible to produce a concentration beyond this limit. In the diabetic this controlling mechanism is absent or inefficient, so that comparatively small quantities of carbohydrate easily result in a blood-sugar concentration considerably above the threshold value, with the consequent production of glycosuria. Whenever a patient with a normal renal threshold for sugar suffers from glycosuria, we know that the blood-sugar is at any rate over 0·18 per cent. On the other hand, it is obvious that a diabetic may have a blood-sugar concentration in the neighbourhood of 0·18 per cent. (just below the threshold value) without giving any indication of this in the urine. Patients with a blood-sugar higher than normal, but below the renal threshold, are, of course, very liable to show intermittent glycosuria after meals, for at this time the blood-sugar shoots up and consequently reaches a point at which the kidneys excrete sugar. A later sample of urine may be quite free from sugar, since the blood-sugar will now

probably have fallen below the threshold value. Any individual with a tendency to pass sugar is more likely to have glycosuria an hour or two after meals than at any other time of the day, and it is not uncommon for patients with mild glycosuria to pass a urine containing as much as 1 per cent. or more of sugar about 2 hours after meals, while the next specimen may be entirely sugar-free. Thus, patients undergoing medical examination for insurance or other purposes are presenting hostages to fortune when, as so frequently happens, they fortify themselves with a large lunch immediately before examination. No better method for bringing out glycosuria could be suggested, but the significance of these points, especially with regard to the quick disappearance of the glycosuria in many cases, has hardly been grasped by those responsible for carrying out urinary examinations. In glycosuric patients it is frequently a matter of chance whether or not the glycosuria is detected, and this explains the difficulty which so frequently puzzles such patients. They are told by one doctor that sugar is present in the urine, and that treatment is advisable; another doctor, equally competent, assures them that no sugar is present. Everything, of course, depends on the relation of the specimen examined to the last meal taken, and in special examinations for glycosuria the patient ought to be told to have a moderate carbohydrate meal from 1 to 2 hours before presenting himself for examination. Immediately before this meal he should empty his bladder, and the next specimen passed 1 to 2 hours after the meal should be the one used for the examination. If no sugar is passed under these conditions it may be assumed that the individual's carbohydrate metabolism is normal.

These observations also indicate the futility of relying on a single estimation of blood-sugar unless the time and nature of the last meal is known, for, as already indicated (p. 28), changes in blood-sugar similar to those obtained after the ingestion of sugars are found after ordinary mixed meals.

In all cases of glycosuria one of two conditions must be present: (1) Either there is hyperglycæmia in excess of the normal threshold value, or (2) the blood-sugar behaves quite normally, but the kidney permits the escape of sugar at a lower level of blood-sugar concentration than is normally the case. In other words, the renal threshold for sugar is lowered. This condition, which is fully discussed later, is known as renal glycosuria. Very occasionally one comes across a patient in whom both factors are operative at the same time. In some elderly diabetic patients suffering from renal changes, it is not uncommon to find the threshold for sugar raised much above the normal. The blood of such patients may contain as much as 0·3 per cent. sugar or more without glycosuria being produced. Obviously, in these patients, examination of the urine gives no indication of the true condition.

Sugar Tolerance Tests in Glycosuria.

The most satisfactory intimation as to the nature of the glycosuria in any case is obtained by giving the patient a certain amount of sugar by the mouth and ascertaining the subsequent changes in blood-sugar concentration. After experimenting with various amounts of different sugars and examining the blood at frequent intervals, I have come to the conclusion that a sugar tolerance test carried out on the following lines gives all the information necessary.

Method of Carrying out Sugar Tolerance Test.

The patient is asked to pass water, a sample of blood being taken for sugar estimation. He then receives a dose of 50 grams* of ordinary good commercial glucose dissolved in 150 c.c. of water. Samples of blood are taken at intervals of ½ hour for 2 hours, while urine is passed at the end of each hour. The nature of the blood-sugar

* Some observers use 100 grams or more, but 50 grams are ample for all purposes.

curve obtained, taken in conjunction with the results of urinary examination, affords us much information, and frequently helps to determine whether or not the patient is suffering from diabetes. When possible, the test should be carried out at least 2 hours after the last meal. In normal individuals the blood-sugar should attain its original level (about 0·1 per cent.) in from 1½ to 2 hours, and the highest point of the curve should not exceed about 0·18 per cent. In old people the return to normal may take 3 hours or so, but any longer period gives rise to suspicion.

In this connection some results obtained by Porter and Langley* are interesting. These observers examined fifty normal individuals on the following plan.

Ten cases in each decade, starting at thirty to forty, of mixed men and women were taken. Each case was starved overnight and the starving blood-sugar level estimated; 50 grams glucose in 100 c.c. water were then given, and the blood-sugar estimated at the end of each ½ hour for 2½ hours, the urine being examined at the expiration of that time. The following table gives the results of these tests.

TABLE I.

Age.	1	2	3	4	5	6
	Before.	½ *hr.*	1 *hr.*	1½ *hrs.*	2 *hrs.*	2½ *hrs.*
Under 30	0·080	0·170	0·125	0·080	0·080	0·080
30–40	0·105	0·184	0·174	0·153	0·150	0·140
40–50	0·120	0·192	0·207	0·165	0·155	0·152
50–60	0·146	0·225	0·218	0·195	0·166	0·155
60–70	0·145	0·225	0·238	0·245	0·205	0·185
70–80	0·115	0·175	0·190	0·185	0·165	0·130

The curves obtained in these patients appear to demonstrate the following points. (1) That the starving blood-sugar level tends to rise from the normal 0·08 per cent. of

* Porter and Langley, *Lancet*, October, 1926, p. 947.

youth to nearly 0·15 per cent. at seventy years of age. (2) That the actual increment of sugar-content of the blood, however, remains the same and is always less than 0·1 per cent. (3) That at the ages considered the highest point of sugar concentration is liable to be reached at the end of 1 hour, rather than at the end of ½ hour as is usual in youth. (4) That there is an increasing delay in return to the starving level, which fails to occur in the 2½-hour period of observation. (5) That in the decade thirty to forty years of age urinary sugar in response to 50 grams glucose is not found, but in the decades above this glycosuria in response to this amount of sugar occurs in about 30 per cent. of tests, being rather higher in the decade sixty to seventy years of age, when it is nearly 40 per cent. (6) In the decade seventy to eighty the type of curve obtained differs greatly in that it does not rise so high, but takes considerably longer to return to starving level. No explanation of this is offered, but the patients were senile.

It must be emphasised, however, that it is quite common for patients from thirty to fifty years to give sugar-curves similar to those given in young patients under thirty.

Results obtained with Sugar Tolerance Tests in Diabetes.

When the curve obtained from a severe case of diabetes is compared with the normal (see p. 20) two important differences are observed. In the diabetic, blood-sugar concentration rises much higher, and far exceeds the threshold value, giving rise to glycosuria; it also requires a much longer time for the blood-sugar to return to its normal level, so that the characteristic curve is high and long drawn out. Though these two features are present to a very considerable degree in severe diabetes, perhaps the most characteristic feature in mild or early cases is the delay in the return of the blood-sugar to its normal level.

The marked effect of sugar ingestion in the moderately

severe type of diabetes is illustrated in Chart 7, which shows the result after giving 25 grams of carbohydrate (potatoes).

Before the upper curve was taken the patient had been receiving a diet which was slightly in excess of his tolerance level for carbohydrates. The blood-sugar before the test was in consequence high. The lower curve was

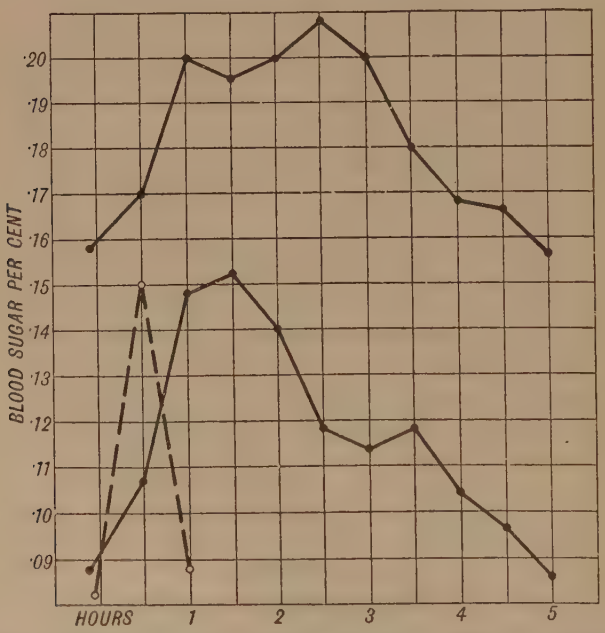

Chart 7.—Showing Behaviour of Blood-Sugar in Moderately Severe Diabetes after Ingestion of 25 Grams Potatoes. Lower Dotted Curve shows Result obtained with 25 Grams Potatoes on the Normal Subject.

obtained after two days' starvation, which had reduced his blood-sugar to a low level. In both, the initial level is not regained until 5 hours have elapsed, showing that a very definite defect was present. The preceding period of starvation had no effect on the length of the curve, and only minor differences are noticed between the curves starting from the initial low blood-sugar and the curve at the beginning of which the blood-sugar was high.

For purposes of comparison a normal curve following the ingestion of 25 grams potatoes is given. In this patient the ingestion of a little more carbohydrate would have easily raised the blood-sugar content very much above the threshold value, while no amount of potatoes would bring about this effect in the normal individual. Though protein raises the blood-sugar and increases the glycosuria in diabetes, the production of sugar is apparently so gradual that no immediate difference in blood-sugar can be obtained as the result of protein feeding, even in advanced diabetes. Chart 8 shows curves obtained from a very severe case with 25 grams of glucose and with 250 grams of meat. The ingestion of protein was practically without effect on the blood-sugar, the very slight variations indicated being well within the limits of experimental error.

Though naturally no tolerance tests are required for diagnosis in severe cases of diabetes, they are of value in ascertaining the degree of severity and the effects of treatment. A very good idea of the gravity of any case can be obtained by carrying out a sugar test with 50 grams of glucose immediately after the modern fasting treatment now in general use has resulted in reducing the blood-sugar to the region of the normal figure. A high and prolonged curve at this stage indicates a severe case. After dietetic treatment, and when the blood-sugar is about the same level as in the earlier test, another test should be carried out, when it may be found that the curve is neither so high nor so prolonged as before, indicating an improvement of the sugar metabolism. A tolerance test carried out immediately after reduction of the blood-sugar by starvation or other means affords an excellent index of the probable prognosis, but the test is only of value after the blood-sugar has been brought as near to the normal level as possible. Not infrequently it will be found that cases of apparently very great severity, with extensive polyuria, accompanied by the passage of very large amounts of sugar, acetone, and

diacetic acid, will rapidly respond to starvation treatment, and show in a few days a fasting blood-sugar very little if any above the normal value. This rapid decrease in blood-sugar and the consequent decrease or elimination of glycosuria affords, in many instances, little or no evidence

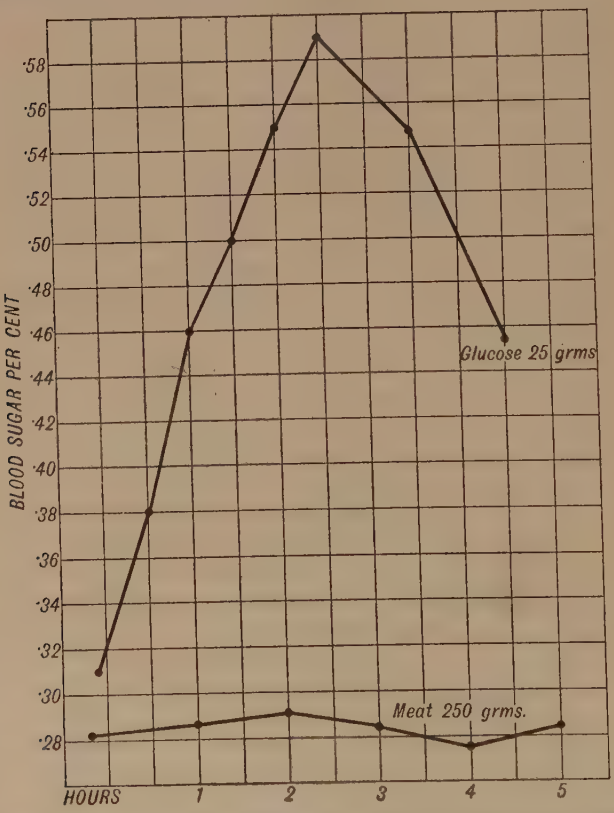

Chart 8.—Showing that Meat has No Immediate Effect in raising the Blood-Sugar Content in Diabetes.

as to the gravity of the condition. If, however, a tolerance test is carried out at this time, a good idea of the real severity of the case, as well as much evidence as to the probable prognosis, can frequently be obtained. A comparison of subsequent tests with this one will show the effect of treatment. It is quite wrong, however, as

is sometimes done, to test an apparently severe case when the blood-sugar is still high, and to compare the result with the curve obtained after treatment, when the blood-sugar may be normal or nearly so. No inference whatever can be drawn from such comparisons, and frequently, when marked improvement is apparent under such conditions, it will be found on closer investigation that no improvement whatever is demonstrated. Indeed, if curves be drawn, and one superimposed on the other, it will often be found that both curves are identical both as to height and prolongation. Here the apparent improvement is dependent on the differences in blood-sugar content at the beginning of the tolerance tests (see p. 34).

The Value of Tolerance Tests in Mild Diabetes.

In mild early cases of diabetes there may be little or no glycosuria, but frequently a definite delay in storage

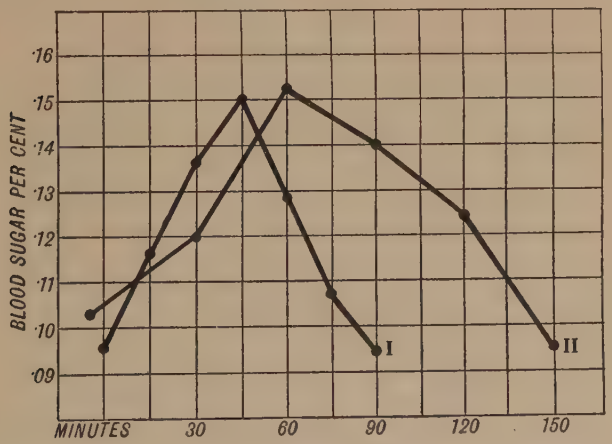

Chart 9.—Curve II. shows Slight Defect in Storage after Dose of 25 Grams Glucose. In Curve I. the Effct of 25 Grams Glucose on a Normal Individual is given.

capacity, resulting in a prolongation of the curve, may be detected. Here there is no definite glycosuria, for the blood-sugar content does not rise above the renal threshold for sugar. In Chart 9 is shown the blood-sugar curve

following the ingestion of 25 grams of glucose in a patient aged twenty-five years in whom occasional intermittent glycosuria had been noticed at intervals for two years.

No evidence of acidosis or other signs of diabetes were observed. As contrasted with the normal curve given in the same chart, a definite defect in storage appears to be present. The fall is considerably slower, and the blood-sugar regains its original level an hour later than in health. Though the actual height of the curve does not exceed the normal, and though no glycosuria occurred throughout the test, the gradual and delayed fall suggest that a minor degree of deficiency was present. It is interesting that the general health of this patient was considerably improved as the result of a limitation of the carbohydrate in the diet. While such a delay in storage is always suspicious in a young person, it would, of course, be of no great significance in an old patient.

In Chart 10 two curves obtained from suspected cases of diabetes are contrasted. The dotted curve gives the result of the ingestion of 50 grams of glucose by a girl of seventeen in whose urine a reducing substance was constantly present. Here the hyperglycæmia seemed to run an absolutely normal course, the fall of the curve was abrupt and rapid, and no suggestion of a failure in the storage mechanism was present. The reducing substance proved to consist mainly of a pentose. The upper curve shows a failure to deal adequately with the 50 grams of glucose ingested. Though the rise in the blood-sugar is not so marked as in many cases of definite diabetes, yet it is undoubtedly excessive, and provokes but a poor response from the storage mechanism. The fall is slow, gradual, and still incomplete at the end of $2\frac{1}{2}$ hours. Glucose and traces of acetone were frequently found in the urine of this patient when on a full diet. There is no doubt that a grave defect was present. In such milder types of glycosuria the value of an examination of the blood-sugar curve following the ingestion of sugar is undoubted, and gives useful indications as to the necessity for treatment.

All patients showing a considerable delay in the return of the blood-sugar to normal after the ingestion of glucose should be regarded with suspicion. This delay appears to be the first effect noticed in early diabetes. Very soon, if the condition progresses, the delay is associated with an abnormal rise in the curve, and any patient showing this combination of a high and a prolonged curve should be regarded as a potential diabetic and treated accord-

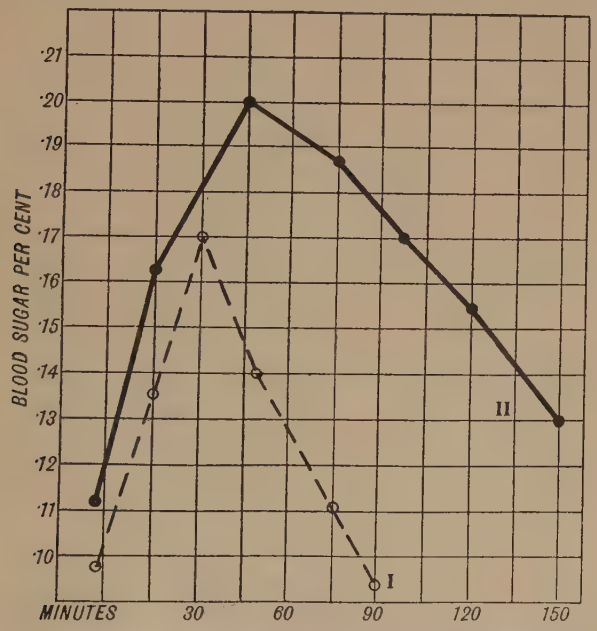

CHART 10.—CURVES FROM TWO CASES OF GLYCOSURIA. No. I. IS NORMAL, WHILE No. II. SHOWS CONSIDERABLE DELAY IN STORAGE. 50 GRAMS GLUCOSE WERE GIVEN IN EACH CASE.

ingly, unless some definite cause for the abnormality can be ascertained. Cases of this nature may, of course, be found in other conditions than diabetes, but at present there is no means of differentiating between them. In certain other types of curves associated with glycosuria the condition is frequently of no importance, and the patient may be assured that no treatment is required.

Much discussion has arisen in the past as to whether

the glycosuria and hyperglycæmia of diabetes are due to an inability on the part of the organism to use sugar, or are the result of excessive sugar production. That the diabetic has lost to a very great extent the power to utilise sugar is certain, but it would appear that the first change that arises in diabetes is the difficulty of storing sugar. This mechanism may be markedly depressed long before any of the ordinary symptoms of diabetes are present, and it would seem that the loss of power of the body to utilise sugar, which appears later on, must in some way be connected with this inability to store sugar. It is possible that ordinary glucose, *as such*, is not changed into glycogen or utilised directly by the organism at all, but that before this happens, the glucose must be changed by a rearrangement of its molecular structure. That such changes take place in the body is probable, and is supported by the work of Hewitt and Pryde,* who brought forward some evidence in favour of the view that the living intestine can produce from ordinary glucose a certain amount of a stereochemical modification known chemically as γ-glucose. If we assume that ordinary glucose must be changed into some isomeric form before it can be built into glycogen or utilised by the body, many of the difficulties associated with the problem of carbohydrate metabolism disappear. At present such ideas are purely speculative, but it is possible that the key to the problem of diabetic chemistry may be found by investigation along these lines. In spite of the large amount of work that has been carried out recently on the nature of the blood-sugar, the question must still be regarded as unsettled.

Some Results obtained by Sugar Tolerance Tests in Diabetes.

The following figures are given as indicating the nature of the results obtained in suspected diabetes cases. The majority of the patients were examined for official pur-

* *Biochemical Journal*, 1920, **14**, 395.

poses, and the glycosuria discovered then for the first time.

Case I.—A naval officer aged thirty-seven. Urine after test contained 1·2 per cent. of sugar and some acetone. A specimen of urine could not be obtained before the test.

	Per Cent.
Blood-sugar before giving glucose	=0·112
,, ,, ½ hour after 50 grams glucose	=0·290
,, ,, 1 ,, ,, ,, ,,	=0·218
,, ,, 1¾ hours ,, ,, ,,	=0·146
,, ,, 2½ ,, ,, ,, ,,	=0·140

Interpretation of Test.—Storage capacity markedly defective; result should be regarded as suspicious of early diabetes, and patient treated accordingly.

Case II.—A man of fifty-four years whose general condition did not appear to be very good. He had not been feeling very fit recently, but did not complain of any definite diabetic symptoms. Urine contained acetone in fair amount. Glycosuria amounted to 4·5 per cent. sugar before test and 6·5 per cent. after the test.

	Per Cent.
Blood-sugar before giving glucose	=0·41
,, ,, ½ hour after 50 grams glucose	=0·49
,, ,, 1½ hours ,, ,, ,,	=0·52
,, ,, 2 ,, ,, ,, ,,	=0·55

Interpretation of Test.—Case of diabetes.

Case III.—A well-built man of forty-nine years. Patient had no symptoms, but urine had a trace of acetone. Before test urine contained traces of sugar; urine passed after test contained 2·4 per cent. sugar.

	Per Cent.
Blood-sugar before giving glucose	=0·125
,, ,, ½ hour after 50 grams glucose	=0·181
,, ,, 1 ,, ,, ,, ,,	=0·240
,, ,, 2 hours ,, ,, ,,	=0·196

Interpretation of Test.—Sugar tolerance not good; should be treated as a suspected case of early diabetes.

Case IV.—Military man, aged sixty-five years, who

appeared to be in fairly good health. Urine before test contained 3 per cent. sugar, while after test 5·4 per cent. was present. No acetone.

	Per Cent.
Blood-sugar before giving glucose	=0·25
,, ,, ½ hour after 50 grams glucose	=0·41
,, ,, 1 ,, ,, ,, ,,	=0·43
,, ,, 1½ hours ,, ,, ,,	=0·38
,, ,, 2 ,, ,, ,, ,,	=0·35

Interpretation of Test.—Should be regarded as a case of diabetes; probably, owing to patient's age, not likely to be very progressive.

Case V.—A clerk, aged twenty-five years, who had been feeling somewhat out of sorts for some time. Sugar was found by his medical man a month before test was carried out. No acetone present. Patient was on modified diet.

	Per Cent.
Blood-sugar before giving glucose	=0·11
,, ,, ½ hour after 50 grams glucose	=0·16
,, ,, 1 ,, ,, ,, ,,	=0·24
,, ,, 1½ hours ,, ,, ,,	=0·18
,, ,, 2 ,, ,, ,, ,,	=0·17
,, ,, 2½ ,, ,, ,, ,,	=0·15

Interpretation of Test.—Such a marked disturbance of sugar storage capacity in a young patient almost certainly indicates a diabetic condition.

Case VI.—A military man, aged fifty-seven, who had spent a good deal of his life abroad. With the exception of some slight polyuria and thirst, no suggestive symptoms were present. Urine before the test gave a faint reaction with Fehling's solution, while the specimen passed after the test contained 3·5 per cent. sugar. A small amount of acetone was present.

	Per Cent.
Blood-sugar before giving glucose	=0·169
,, ,, ½ hour after 50 grams glucose	=0·210
,, ,, 1 ,, ,, ,, ,,	=0·240
,, ,, 2 hours ,, ,, ,,	=0·160

Interpretation of Test.—Though patient is an elderly man, the marked diminution in sugar tolerance must be regarded as an indication of potential diabetes.

These results indicate the kind of figures obtained in patients in whom the diagnosis is not very clear until blood-sugar and sugar tolerance tests are done. The very marked difference between these and certain other cases of glycosuria described below is very striking.

Some Anomalous Sugar Tolerance Curves in Glycosuric Patients.

Though the typical diabetic curve is higher and more prolonged than the normal, there is reason to believe that the very early stages of diabetes may be indicated by a curve normal as to height, and only differing from the normal in being more prolonged. Generally, these two phenomena go together, but whatever the nature of the curve obtained in any given case, one usually assumes that if after the ingestion of 50 grams of glucose the blood-sugar returns to the neighbourhood of 0·1 per cent. or so within two hours there is not much the matter. Sometimes, however, very marked glycosuria is found in patients whose blood-sugar is quite low in less than two hours after the glucose is taken. Certain of these are, of course, cases of " leaky " kidneys, but, occasionally, this is not so, and in such cases the sugar tolerance curve is found to be of a very peculiar type. Unless the blood-sugar is estimated shortly after meals it is generally found to be normal before the test glucose is given, but within an hour it shoots right up over the threshold value to perhaps 0·22 to 0·23 per cent. In this it resembles an ordinary mild diabetic curve, but this rise, instead of being prolonged in the typical manner associated with diabetes, is quickly followed by a sharp descent, so that the blood-sugar very soon returns to normal, just as happens in an ordinary healthy patient. Such a curve is represented in Chart 11. The patient passed urine containing 1·8 per cent. sugar after the test, and

a sample taken before the test gave a slight reaction with Fehling's solution. Here the blood-sugar, which was 0·1 per cent. to begin with, rose quickly to 0·214 per cent. in ½ hour. After 1 hour it was 0·154 per cent., and in 1½ hours it had dropped to 0·098 per cent. The ability to get rid of the increased blood-sugar and to return to a normal blood-sugar value within a limited period after a sugar test is undoubtedly the best indication of an effective carbohydrate metabolism. This power,

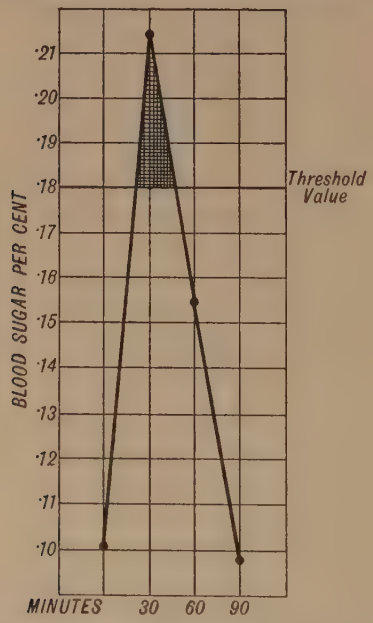

CHART 11.—SHOWING TYPICAL "LAG" CURVE.

when normal, is generally associated with a well-developed mechanism, which prevents the blood-sugar from rising above the threshold value even when a large amount of sugar is taken. In the cases now described this mechanism appears to be in abeyance, so that on the ingestion of sugar the blood-sugar rises to a point at which glycosuria is produced. If we take 0·18 per cent. as the approximate threshold value for sugar, a reference to the chart shows that during the test the blood-sugar

remained at a concentration of over 0·18 per cent. for about 35 to 40 minutes, during which time sugar would have been continuously excreted.

The interpretation of this particular type of curve is difficult. It would seem as if the mechanism for keeping the blood-sugar below the threshold value was later than usual in exerting itself, but that general carbohydrate storage was quite efficient. In practically all the cases of this nature that I have seen the maximum concentration of blood-sugar was obtained in the first half-hour, so that very rapid absorption must have been taking place. Whether or not we can regard this phenomenon as being connected with extremely rapid absorption of the sugar which temporarily overwhelms the inhibiting mechanism is not known, but, at any rate, the phenomenon seems to be dependent on a delay in the intervention of this mechanism. When the mechanism does get to work it seems to be quite effective, but for some reason it becomes operative a little later than usual, with the result that the blood-sugar is allowed to rise above the point at which sugar is excreted in the urine. Theoretically, we would not expect this anomalous behaviour to be of much importance from the prognostic point of view, and this seems to be the correct view to take in the majority of cases. At present, it is impossible to say with certainty what the condition indicates, but, on the whole, it would seem to be of little importance. I have recently examined a man who gave a history of glycosuria extending over twenty years; he gave the typical sugar tolerance curve of the type described. This patient was a naval officer, forty-five years of age, who had served in the North Sea during the late war without having to report sick on any occasion. He told me that he felt quite well, but knew that sugar was found in his urine when he was about twenty years of age, and on several occasions afterwards, though he had never suffered any inconvenience on this account. He was a powerful, well-built, muscular man who seemed to be in

robust health. A sugar tolerance test with 50 grams of glucose gave the following result. Before taking the sugar the urine contained 0·8 per cent. sugar, and after the test 1·8 per cent.

	Per Cent.
Blood-sugar before taking glucose	=0·104
,, ,, ½ hour after glucose	=0·224
,, ,, 1 ,, ,, ,,	=0·132
,, ,, 1½ hours ,, ,,	=0·106

Here the sugar storage seemed to be excellent, and the fact that at one point a blood-sugar of 0·224 per cent. was reached can hardly be regarded as very important in view of the history of the case.

It is possible that this type of curve, which for convenience may be referred to as the "lag" curve, may be produced by different factors, for some investigators have stated that the condition may possibly pass into a true diabetes. I have seen one case of diabetes in a child where the chief feature of the curve was its sharp and quick rise, but some slight prolongation was present as well. Generally speaking, it is probable that in the great majority of cases these "lag" curves do not indicate a potential diabetic condition. For the present I take the view that a patient who gives this lag type of curve, but *who shows no delay in the return of blood-sugar to normal after ingesting sugar*, is probably not suffering from a defect which is likely to prove prejudicial to his carbohydrate metabolism.

The figures in Table II. on p. 47 were obtained in cases examined recently by me.

The first patient had not been feeling very well, and on routine examination of his urine sugar was found; no symptoms pointing to the presence of diabetes were present, but his medical adviser had placed him on a starch-free diet a short time before his sugar tolerance test was done. Traces of acetone found in his urine were probably the result of his large protein and fat diet. In the case of the other subjects sugar was found

during the course of an official medical examination in connection with pension allowances. Each individual received the usual dose of 50 grams glucose. In each instance a favourable view of the condition was taken.

TABLE II.

Number of patient ..	1	2	3	4	5
Patient's age ..	54	40	42	35	28
Blood-sugar per cent.					
before test ..	0·102	0·125	0·118	0·116	0·096
After ½ hour ..	0·205	0·212	0·216	0·205	0·196
„ 1 „ ..	0·168	0·180	0·181	0·116	0·180
„ 1½ hours ..	0·112	0·090	—	0·085	—
„ 2 „ ..	0·109	—	0·125	—	0·110
Urine sugar per cent.					
before test ..	ces	Traces	0·5	Traces	Traces
After test	Tra	0·7	3·0	1·1	0·5

RENAL GLYCOSURIA.

The next type of case to be discussed is essentially different in nature from those already described. Whatever divergence of opinion may exist as to the significance of sugar tolerance curves in the above conditions, it is now well established that so-called renal glycosuria has essentially no connection with diabetes, and does no harm whatever to the patient. In renal glycosuria the kidney threshold for sugar is lower than normal, and so the usual rise in blood-sugar following the ingestion of carbohydrates produces glycosuria. Thus, if the kidneys tend to pass sugar when the blood-sugar rises to 0·14 per cent. or less, sugar will probably be passed in the urine after each ordinary mixed meal, for, as has been already shown, the blood-sugar in the normal individual generally rises to a higher level than this after a meal. Renal glycosuria means simply that the kidneys allow sugar to pass through into the urine at a lower level of blood-sugar

concentration than usual, and this level may be at any point between the normal threshold of approximately 0·18 per cent. and the usual fasting level of about 0·1 per cent. This condition, which is sometimes referred to as "leaky" kidneys, is certainly much more common than is usually believed, and many cases of long-standing glycosuria will, on examination, be found to be of this nature. In these renal cases the sugar tolerance curve is quite typical, for the highest point never exceeds the normal threshold, and frequently the rise is very much

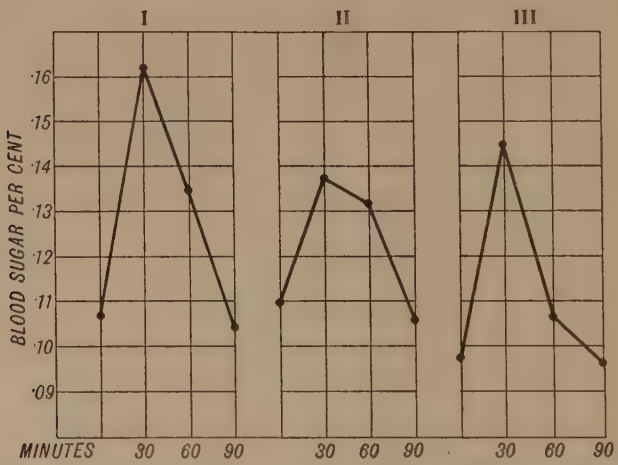

Chart 12.—Showing Some Curves obtained from Patients with Renal Glycosuria.

less than normal. This is dependent on the fact that sugar, which would normally accumulate in the blood, and so raise the blood-sugar concentration, is thrown out in the urine. Consequently, some curves of renal glycosuria may not show a higher maximum value than 0·13 or 0·14 per cent. of blood-sugar. In other respects the curve behaves just as the normal does. The blood-sugar returns to the normal level in from $1\frac{1}{2}$ to 2 hours, or perhaps earlier, and the glycosuria ceases to appear until after the next starchy meal.

Chart 12 shows three curves from typical cases of

renal glycosuria. In these patients the urine gave no reaction for sugar before the test, but considerable glycosuria was present afterwards. As usual, 50 grams of glucose were used for the test.

TABLE III.

CASES OF "RENAL" GLYCOSURIA.

Number of patient	1	2	3	4	5	6	7	8	9
Age	49	43	58	63	50	50	35	35	19
Blood-sugar per cent. before test	0·108	0·106	0·112	0·116	0·123	0·100	0·100	0·112	0·102
After ½ hour	0·176	0·158	0·154	0·168	0·187	0·152	0·108	0·162	0·147
,, 1 ,,	0·112	0·100	0·138	0·131	0·167	0·121	0·131	0·087	0·121
,, 1½ hours	0·109	0·090	0·128	0·090	0·121	0·091	0·100	0·090	0·089
,, 2 ,,	—	—	—	—	0·105	—	0·084	—	—
Urine Sugar per cent. before test	0·3	—	Traces	—	0·7	0·5	—	Present	Traces
After test ..	3·5	3·0	2·5	0·6	1·3	2·5	1·2	Present	0·9

That the condition is harmless seems to be proved by the fact that several patients have been examined who are known to have had glycosuria for many years. The slight loss of carbohydrate may be a disadvantage, but practically this is never so great as to be of much importance. It is possible, of course, for a diabetic to have a lowered renal threshold, but this condition must be rare; in such a case, however, the usual high and prolonged curve would be found, and any evidence of increased renal permeability would naturally be masked and very hard to find. In one patient under my care suffering from moderately severe diabetes, the persistence of glycosuria, with low blood-sugar content, led to a careful investigation of the underlying condition, with the result that he was found to pass sugar whenever the blood-sugar approached the region of 0·14 per cent. In such cases the urine gives no real indication as to the effect of treatment on the true

diabetic condition, for the tendency for glycosuria is much more marked than it is in the ordinary diabetic with a normal threshold value. Obviously, as the result of complete or partial withdrawal of carbohydrate from the diet, the renal glycosuria will disappear, but a very small amount indeed of carbohydrate may bring it on again, especially in cases with a very low sugar threshold. Table III. (p. 49) gives the results of sugar tolerance tests in several cases of renal glycosuria examined by me.

ON SO-CALLED ALIMENTARY GLYCOSURIA.

Practically all the textbooks dealing with glycosuria refer to a supposed variety of this condition, which they designate as "alimentary glycosuria." The idea is that the absorption of a large amount of sugar from the intestine may result in an overflow into the blood-stream, and consequent glycosuria; this is said to occur in patients in whom no defect of carbohydrate metabolism is present. From what has already been stated regarding blood-sugar, it will be obvious to the reader that no essential difference exists between "alimentary glycosuria" and other glycosurias, and the term might with advantage be dropped. The extreme difficulty of overcoming the normal storage mechanism in the healthy individual has frequently been insisted on, and whenever glycosuria occurs in a patient with a normal renal threshold for sugar it always indicates some abnormality in this mechanism. Alimentary glycosuria is essentially of the same nature as the glycosuria of diabetes in so far as it indicates, in both cases, some change in the normal mechanism for dealing with carbohydrates. Glycosuria following a large dose of ingested sugar must not be considered as analogous to an increase of urea in the urine after taking a large quantity of urea. In the latter case the urea passes into the blood without being influenced by any storing mechanism, and it consequently increases the amount of urea excreted. In the case of sugar the normal storing mechanism should be

sufficiently active to prevent almost any amount of ingested sugar from raising the blood-sugar to the point at which glycosuria is produced.

Some General Observations on Glycosuria.

The large amount of diabetic literature appearing in modern times has perhaps resulted in too much attention being attached to glycosuria. Glycosuria, like albuminuria, may be an important feature, or it may be of little significance; it bears roughly the same relationship to diabetes as albuminuria does to nephritis. Glycosuria is relatively common, while diabetes is, on the whole, a comparatively rare disease. This must mean that glycosuria has frequently no relationship to diabetes, just as albuminuria is no definite indication of the presence of nephritis. Both conditions, when found, should be regarded as possibly important symptoms, but in neither case should the medical adviser rest contented until he has done all that is possible to ascertain the true import of the symptom. It is advisable to regard every patient with glycosuria as a potential diabetic, but this does not mean that the patient should be told that he has diabetes and that diabetic treatment should be instituted. This attitude is unfortunately too common, and frequently results in inflicting a considerable amount of quite unnecessary worry and discomfort on the unfortunate patient. On finding glycosuria, it should be the duty of every medical man to have an investigation carried out by means of the sugar tolerance test described. If this were more frequently done, many of these cases would be found to be quite unimportant. There is now no excuse for treating all patients with glycosuria as diabetics, but experience shows that this is still frequently done by many practitioners. Perhaps they are not altogether to blame, for recent writers on the subject of diabetes are all too prone to suggest this attitude. It is, of course, most important that all cases of diabetes should be treated at the earliest possible moment, for this gives the best chance

to the patient, but it is equally important that the practitioner should ascertain, as far as he can do so by the methods now available, whether the condition really is to be regarded as potential diabetes or not. Again and again I have seen patients suffering from nothing more alarming than simple innocuous renal glycosuria, who were subjected to most drastic antidiabetic treatment, much to their physical and mental detriment. Indeed, the last patient with glycosuria I saw, before writing this, was a young man of twenty-five who had consulted his doctor on account of some digestive trouble. In the course of the usual routine examination of the urine, sugar was discovered and diabetes diagnosed. The patient was starved and subjected to the usual régime, but whenever an attempt was made to add even comparatively small amounts of carbohydrate to the diet, glycosuria returned. The apparent lack of response to treatment suggested a bad prognosis to his medical man, and the patient, when seen by me, was in the depth of depression and despair. When, as the result of a blood-sugar test, I told him that he had no diabetes, and that his symptoms were of no importance, the good news almost overwhelmed him. With 50 grams of glucose his test gave the following figures:

Blood before test	=	0·100	per cent. glucose.
Blood ½ hour after glucose	=	0·150	,, ,,
,, 1 ,, ,, ,,	=	0·112	,, ,,
,, 1¼ hours ,, ,,	=	0·092	,, ,,

The urine contained small traces of sugar to begin with, and after 1 hour about 1·5 per cent. was present. The next specimen obtained after 1½ hours gave only a very faint reaction with Fehling's solution.

By the use of modern methods these tragedies can always be prevented.

Some Records of Cases.

On looking up my records for the last two years, I find that I have notes of the investigation of forty-eight cases of glycosuria. In all these patients the condition was

found in the course of routine examination of the urine either for official or general medical purposes, and no patient gave a history suggesting the presence of diabetes. They were all of the type of case that gives so much trouble to the practitioner. The majority of them were first seen by a distinguished London physician of very great experience, who, finding glycosuria present, sent them for further investigation.

Examination showed that no less than twenty-three of these patients suffered from definite renal glycosuria; in nine the curve obtained was of the "lag" variety (p. 43), and a favourable opinion was given; ten gave a curve of the ordinary diabetic type, while in three the result of examination was difficult to interpret, but the condition did not appear to be serious. In three the reducing substance present did not ferment with yeast, and was not glucose. These very interesting results are expressed in tabular form in Table IV.

TABLE IV.

Total Number Examined.	*Number with Renal Type Curve.*	*Per Cent. of Total Number showing Renal Curve.*	*Number with "Lag" Curve.*	*Per Cent. of Total Number showing "Lag" Curve.*	*Number with Diabetic Curve.*	*Per Cent. of Total Number showing Diabetic Curve.*
48	23	48	9	19	10	21

These figures bear out the contention that renal glycosuria is much more common than has hitherto been recognised. In the above series practically 50 per cent. of the total number of cases were of this nature, while approximately other 20 per cent. (the "lag" type) were probably of no importance. In slightly over 20 per cent. a high curve with a more or less prolonged delay in the return to normal level was obtained, suggesting definite interference with the storage mechanism for carbohydrates. Such cases, of course, are not necessarily of a diabetic nature, but should be treated as such, since there is no

method known at present by which a more definite diagnosis can be made. In these ten potentially diabetic cases, acetone was present in five, while the urine of one patient contained diacetic acid as well.

These results lend great weight to the conclusion that glycosuria *per se* is probably of no more importance than albuminuria, and that, like albuminuria, the condition is much more common than is generally recognised. Glycosuria may be a negligible manifestation, or it may be of great importance. Experience shows, however, that frequently it is not to be regarded as a serious condition.

CHAPTER IV

SOME PATHOLOGICAL CONDITIONS ASSOCIATED WITH GLYCOSURIA

Of the various clinical conditions associated with glycosuria it is unnecessary to say much here, since they are fully discussed in the ordinary medical textbooks and in special works. As is well known, glycosuria sometimes follows lesions of the central nervous system, a result that is not surprising in the light of Claude Bernard's classical experiment, in which he showed that puncture of the floor of the fourth ventricle in animals causes sugar to appear in the urine.

From the clinical standpoint glycosuria is most frequently found in lesions connected with some of the endocrine glands, but its association with various manifestations such as gout is not uncommon.

The reduction of Fehling's solution by many urines passed after anæsthesia is now known to be due to the temporary presence of sugar, though, for a long time, the phenomenon was supposed to be caused by glycuronic acid. Apparently the production of post-anæsthetic glycosuria depends to a large extent on a deficiency in oxygen supply, for the more marked the tendency to asphyxia the greater is the probability that the urine will contain sugar.

It is generally stated that glycosuria is frequently present in exophthalmic goitre, but in my experience actual glycosuria is not very common in this disease, though there is undoubtedly a marked tendency for some disturbance of carbohydrate metabolism to be present.

This is well brought out by sugar tolerance tests, for in some cases of the disease the curve obtained is decidedly

prolonged, while, in a few, it rises beyond the threshold value, with consequent excretion of sugar. Glycosuria frequently accompanies the irritation stage of acromegaly, but later this may sometimes be succeeded by an increased tolerance for carbohydrates. This increased tolerance, which apparently appears when the pituitary gland undergoes atrophy, does not seem to be so common as is generally believed, for several of the cases that I have had an opportunity of examining reacted to sugar tolerance tests in the normal way. In this connection it must not be forgotten that the test which used to be employed consisted in giving the patient from 100 to 200 grams of glucose and ascertaining, by subsequent examination of the urine, whether glycosuria was produced. From what has already been said it is obvious that this is no real test, because of the impossibility of producing glycosuria in the normal subject even after very excessive doses of sugar are taken. Discussing this problem, Taylor and Hulton* state, as the result of their experimental work, that "in the majority of healthy males there is no limit of assimilation of glucose; glycosuria does not occur following the largest possible ingestion of pure glucose." In five instances these observers gave as much as 500 grams of glucose, with the production of glycosuria in but one case. It is very difficult to give a larger amount than this to any subject, owing to the tendency to nausea and vomiting produced by very large doses. As a rule, such a comparatively large amount as 400 grams of glucose is tolerated quite well, no glycosuria whatever being evident afterwards. From this it would seem that the question of sugar tolerance, in conditions of hypoactivity of the pituitary and other endocrine glands, requires to be reinvestigated. That glycosuria is present in certain cases of hyperactivity of the endocrine glands is accepted by all, but probably it is neither so marked nor so common as is frequently assumed.

As far as we know, it would seem that glycosuria con-

* *Journ. Biol. Chem.*, 1916, 25, 173.

nected with endocrine gland changes is always associated with hyperactivity of these glands, and is not likely to be found in atrophic lesions. This glycosuria may appear in hyperpituitarism and in hyperthyroidism, but is rarely, if ever, seen in conditions such as myxœdema and Frolich's disease, in which the characteristic feature is a lessened activity on the part of the thyroid and pituitary glands respectively. Increased activity of the adrenal glands may also produce glycosuria, while the destruction of these glands, so frequently seen in Addison's disease, may be associated with increased sugar tolerance.

The effect of emotional disturbances and excitement in producing glycosuria is now well recognised, and is of considerable practical importance. An interesting observation bearing on this point was reported in 1914 by Folin, Denis, and Smillie,* who examined the urines of a number of male students after an examination and found sugar in 18 per cent. of them. On extending the experiment to female students no such result was in evidence, but as these latter students were all younger than the males, it is possible that the irresponsibility of youth, rather than any fundamental lack of emotion, was the cause of the difference. Possibly, the glycosuria sometimes found during the medical examination of a patient may be nothing more than an indication of mental excitement and nervousness.

Another cause of glycosuria may not infrequently be found in the excessive use of alcohol; after long dinners, in which alcohol may play but a moderate part, glucose is frequently present in the urine on the following day. The frequency of glycosuria in patients suffering from boils and septic wounds is too well known to require further mention here.

In carrying out tests on patients suffering from glycosuria, an attempt should always be made to eliminate such possible etiological factors as those mentioned above, for excitement, alcohol, or drugs may sometimes

* *Journ. Biol. Chem.*, 1914, 17, 519.

produce a sugar tolerance curve very closely resembling that observed in the early stages of diabetes. A most interesting case of this kind came under my notice a short time ago. The patient was a military man aged fifty-eight, who, on being examined for pension purposes, was found to have very marked glycosuria. Immediately afterwards a sugar tolerance test was done, with the result that a very marked disturbance of the sugar storage mechanism was found. The patient was rather thin, and his general condition did not appear to be very good, but he said that he felt quite well and had no subjective symptoms whatever suggesting diabetes. He denied taking any drugs, and on the whole, in spite of his statement that his health was excellent, I was inclined to the view that probably he was a case of early diabetes. On examining him more carefully, however, his pulse was found to be rather fast, and just as he was leaving the laboratory I made the chance observation, "You are not by any chance taking thyroid?" To my surprise the patient calmly replied that he was doing so. On reminding him that he had already denied taking drugs, he replied that he did not regard thyroid as a drug in the usual sense, and as he was not taking it for medicinal purposes he had quite forgotten all about it. An enquiry as to his reason for taking the drug elicited the curious fact that a friend had told him that in thyroid extract lay the secret of rejuvenescence, and in order to rejuvenate himself and feel young once more he was in the habit of taking two or three, or sometimes more, tablets per day. Thinking that a clue to his condition was now obtained, I asked him to stop taking thyroid altogether for some weeks and then to have another examination. He carried out these instructions, with the result that the glycosuria soon disappeared, and another test done about a fortnight later gave a perfectly normal curve. No suggestion whatever of decreased carbohydrate tolerance could now be found, and no sugar was passed in the urine either before or after the test. A comparison of the figures obtained

in the two tests shows the marked change brought about.

	I. Result while taking Thyroid Extract.	*II. Result a Fortnight Afterwards.*
Blood-sugar before glucose given ..	0·106	0·09
,, ,, ½ hour after glucose ..	0·25	0·17
,, ,, 1 ,, ,, ,, ..	0·17	0·12
,, ,, 1½ hours ,, ,, ..	0·16	0·10
,, ,, 2 ,, ,, ,, ..	0·15	—
	Urine contained 2 per cent. sugar.	Urine sugar-free.

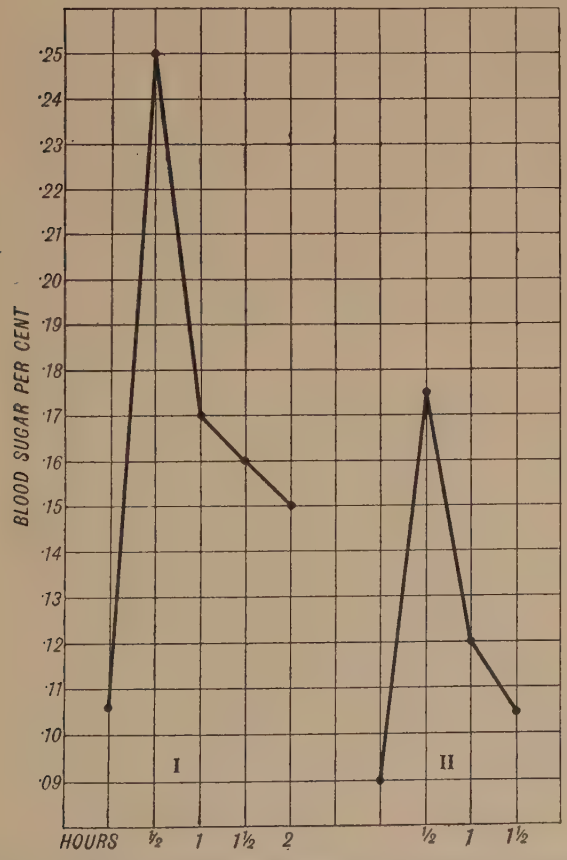

Chart 13.—Curve I. shows Effect of Thyroid Ingestion. Curve II. was obtained a Fortnight after Patient ceased to take Thyroid.

Chart 13 shows the two curves represented by these figures. The marked improvement that took place in a comparatively short time after withdrawal of the thyroid is very impressive. The episode suggests the necessity for careful elimination of possible etiological factors of this nature when cases of glycosuria are being investigated.

CHAPTER V

THE ESTIMATION OF BLOOD-SUGAR

Until recent years the estimation of blood-sugar was a formidable process, but it is now quite a simple procedure which can be carried out by anybody having the most elementary knowledge of chemical methods and manipulation. Several well-known processes are available, but the author's method, as described here, is probably simpler in its application than any other, and possesses the advantage that it does not require the use of a colorimeter. The method has been very extensively tested at St. Thomas's Hospital, and at other laboratories both in this country and in America, and the results of the many thousands of experiments carried out leave no room for doubt that its accuracy is all that can be desired, and is at least equal to that obtained by any of the colorimetric methods now in vogue. The method has been in use since 1915, but various slight changes have been adopted from time to time, so that it is now possible to carry out an accurate estimation in less than 20 minutes.

In estimating the blood-sugar only a very small amount of blood is required, so that samples may be taken as often as necessary without any inconvenience to the patient. The author has carried out estimations on as many as twelve different samples of his own blood in one afternoon. The old method of puncturing a vein of the arm is obviated, and no pain is inflicted on the patient. Experiments showed that the results obtained from 0·2 c.c. of blood were just as accurate as those obtained from 1 or 2 c.c. of blood, so that now 0·2 c.c. is always taken for an estimation.

Though such a small quantity of blood is used, no special skill is necessary, since the method is by no means

a " micro-method " in the sense of necessitating the use of very small quantities of material throughout the procedure. Indeed, with the exception of the blood measurement, no minute quantities of any solution are used, and no greater delicacy of manipulation is really required here than is customary in the ordinary estimation of sugar in urine.

Directions for Estimating Blood-Sugar by Maclean's Method.

The blood is obtained directly from the finger or from the ear. A special pipette (Fig. 2, B) is used to collect and measure the blood. If the finger is used, a piece of rubber tubing is wound round the upper part to cause congestion near the point, and a prick is made with a needle on the back of the finger immediately above the root of the nail. The point of the pipette is placed in contact with the side of the drop, when the blood immediately flows in. The pipette is then held more or less horizontally, or with the distal end somewhat inclined downwards, so that the passage of the blood into the pipette is assisted by gravity. When the blood reaches the mark the pipette is removed, and any blood that may remain on the point is carefully wiped away. If the pipette contains too much blood, the necessary adjustment is made by gently tapping the point against the thumb-nail, when a very little blood will escape. If sufficient blood is not obtained from the first prick, the rubber tube may be removed from the finger and the puncture repeated as often as three times or more without fear of coagulation taking place. All possibility of coagulation may be prevented by dusting a little very finely ground potassium oxalate over the area from which the blood is to be withdrawn. If the prick is made about the centre of this area, the exuding blood comes into contact with the oxalate and coagulation never occurs. Potassium oxalate, however, is not necessary, and I never employ

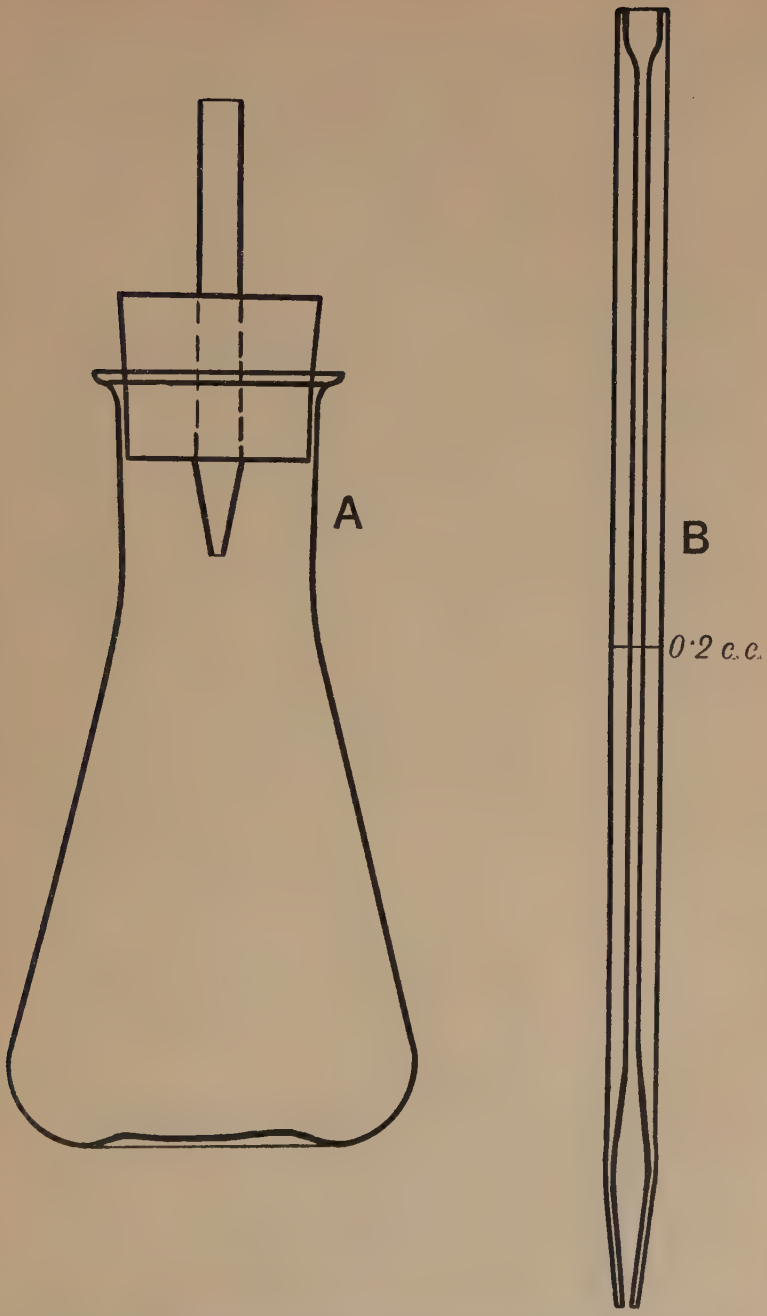

Fig. 2.—*A*, Boiling Flask of Exact Size Used; *B*, Special Pipette for taking 0·2 c.c. Blood.

it now, but its use might possibly prove of some advantage to a beginner. If the hand is cold, it should be placed in hot water for a short time before taking the blood.

The one important point to be observed in using the method is that the pipette should be kept scrupulously clean; if any trace of greasy material is present on the inner surface the blood will not flow. It is, therefore, most important that after each experiment the pipette should be washed out with a hot mixture of sulphuric acid and potassium bichromate. After thorough treatment with this mixture the pipette is washed out with distilled water, followed by alcohol and ether, and then dried by the use of a blowpipe and gentle heat. Personally, after each experiment I place the pipette in a test-tube containing bichromate mixture, and let it stand there until it is again required, when it is treated as described. When these precautions are taken, there is never any difficulty in obtaining exactly 0·2 c.c. of blood.

For carrying out the method the following pieces of apparatus and solutions are required:

1. The special pipette already described made "to contain" 0·2 c.c. blood.*
2. Two burettes of 25 c.c. capacity carefully graduated in $\frac{1}{10}$ c.c.
3. Two Erlenmeyer flasks of 100 c.c. capacity made of hard glass.
4. One 1 c.c. pipette graduated in $\frac{1}{100}$ c.c.
5. One 1 c.c. ordinary pipette.
6. Two 2 c.c. ordinary pipettes.
7. One 5 c.c. ordinary pipette.
8. One 20 c.c. ordinary pipette.
9. One small filtering funnel.
10. One small cylinder or test-tube of about 25 c.c. capacity to hold filtrate.
11. Whatman's filter paper (No. 1, diameter 9 cms.†).
12. Two flasks graduated to hold 200 c.c.

* Obtained from Hawksley and Son, Wigmore Street, London, who can also supply all the other apparatus specified here.

† If very rapid filtration is desired, Whatman's No. 41 filter paper is best.

13. One heat-regulating apparatus described below.
14. A few triangular surgical needles and a piece of rubber tubing.
15. The solutions specified below.

Solutions Required.*

No. 1: *Acid Sodium Sulphate Solution.*—A 15 per cent. solution of sodium sulphate to which acetic acid† is added in the proportion of 0·1 c.c. to each 100 c.c. solution immediately before use. Ordinary B.P. sodium sulphate does quite well, and is preferable to many so-called "pure" samples, which occasionally contain sufficient impurities to interfere with the test. The acid mixture does not keep very long, so it is best to make up fresh solutions when required from stock 15 per cent. sodium sulphate solution. If only a few estimations are being done, it is more convenient to measure out 23·8 c.c. of the stock sodium sulphate, and to add to this 1 drop of 50 per cent. acetic acid.

No. 2: *Dialysed Iron Solution.*—This solution should be submitted to prolonged dialysis until the dialysate gives no reaction with silver nitrate. A suitable solution, "dialysed iron B.D.H.," is supplied by the British Drug Houses.

No. 3: *Solution for Estimating Sugar in Filtrate.*—

Potassium bicarbonate	12	grams
Potassium carbonate (anhyd.) ..	8	,,
Copper sulphate crystals	0·35	,,
Potassium iodate	0·05	,,
Potassium iodide	0·50	,,
Distilled water	to 100	c.c.

In making up this solution 12 grams of potassium bicarbonate are dissolved by gentle heating (temperature not to exceed 37°) in 60 to 70 c.c. distilled water. The potassium carbonate is then added. The copper sulphate is dissolved in a separate beaker in a few c.c. of water, and added to the mixture of carbonates without waiting

* Suitable solutions guaranteed as to accuracy and purity may be obtained from Messrs. Boots, Pure Chemicals Department, Nottingham, who supply complete sets or any one solution. These may be obtained through any branch of Messrs. Boots.

† The acetic acid must be pure, and should be redistilled over potassium permanganate.

for the carbonate to dissolve completely. When the resulting effervescence has passed over, the complete solution of any remaining carbonate is brought about by heat. The iodate and iodide are now added, the solution thoroughly shaken and filtered through a starch-free paper (No. 1 Whatman). The solution keeps indefinitely, but should be allowed to stand for a few days before using it.

This solution must be standardised as regards the amount of free iodine liberated on the addition of excess of acid. This is done by taking about 8 to 10 c.c. acid sodium sulphate solution (No. 1), and adding to this exactly 2 c.c. of the alkaline copper solution; this is made strongly acid by the addition of 2 c.c. of 25 per cent. sulphuric acid. About one minute after effervescence is completed and after the mixture has been thoroughly shaken it is titrated with N/400 sodium thiosulphate solution in the manner described later on when dealing with blood.

Two c.c. of this copper solution should require about 11 c.c. N/400 thiosulphate to take up all the iodine liberated.

No. 4: *An N/400 Sodium Thiosulphate Solution.*— This solution must be freshly prepared when required as it keeps its titre for only a day or two. An N/10 solution, however, when put up in an amber bottle and preserved from light, keeps for many months. The N/400 solution is prepared from an N/10 solution by adding 5 c.c. of the latter to some distilled water in a graduated flask, and making up to 200 c.c.

No. 5: *A solution of "soluble starch" of about 1 per cent. strength.*

No. 6: *A 25 per cent. Solution of Sulphuric Acid.*— This solution is made up by adding 25 c.c. strong sulphuric acid to 75 c.c. distilled water.

Standardising of Heating.

For very accurate estimation of the sugar it is essential that the heating of the blood-filtrate with the copper solution should be standardised. This can easily be done by interposing a small manometer between the gas-tap and the burner (see Fig. 3). If a suitable manometer is not to hand it is very easy to extemporise one, for all that is required is a U-piece with two pieces of bent glass. These can be connected by means of rubber tubing, and are quite as effective as if the whole were

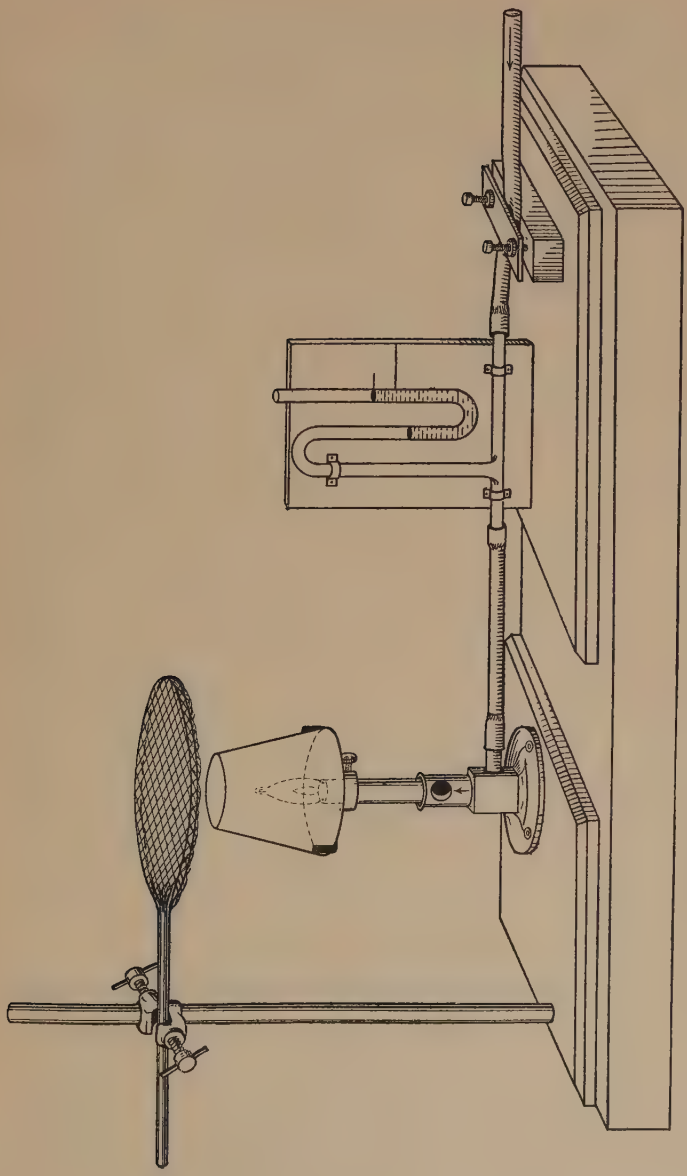

FIG. 3.—SIMPLE ARRANGEMENT FOR REGULATING GAS PRESSURE AND GIVING STANDARD FLAME.

in one part. A piece of strong rubber tubing passing through a screw clip connects the one end of the U-piece with the gas supply, while the other end is connected with the bunsen burner. The burner should have a small chimney to protect the flame. From $\frac{1}{4}$ to $\frac{1}{2}$ inch above this a ring with ordinary wire gauze is supported, on which the flask is boiled. The gauze must be separated by an interval from the chimney, otherwise the gas will not burn properly. When a suitable flame is determined, the position at which the cover of the air inlet cuts the side of the hole in the inner side of the bunsen is marked with a file, as indicated in the diagram, so that the same amount of air can always be admitted by adjusting to this mark. It is perhaps better, however, to fix this outer cover in position by inserting a small wedge between it and the inner tube or by some other means. We are then certain that the air entry is constant. Before proceeding to find a suitable strength of flame, some coloured fluid is put into the manometer through the open end by means of a capillary pipette; the upper surface of this fluid in both limbs is then indicated by a line on a white card placed behind the manometer, or by marks on the two limbs of the manometer itself. When this is done the gas is turned full on, the screw closed down somewhat, and a trial made by placing a 100 c.c. conical Erlenmeyer flask containing 22 c.c. of acid sodium sulphate over the flame. For very exact work the fluid should be first cooled (or warmed) to 20° C. After a few trials a flame is easily found which will bring the solution to vigorous boiling in about 1 minute 40 seconds. This is then controlled by taking 20 c.c. of acid sodium sulphate solution to which are added 2 c.c. of the alkaline copper iodine solution, and testing as before. In each case, of course, the adjustment of the flame is brought about by loosening or tightening the screw clip. When a strength of flame is found that brings the mixture to *distinct boiling* in about 1 minute 40 seconds or so, the position of the fluid in both limbs of the manometer is marked either by ink on the glass or on a white card behind. The regulating mechanism is now complete, and when it is required at a future time all that is necessary is to adjust the gas pressure by means of the screw until the upper surfaces of the coloured liquid stand at the marks indicated. After some time it will be necessary to add some more coloured fluid to compensate for slight

losses due to evaporation. If the gas pressure is liable to variations during an actual experiment the manometer should be watched, and if a change of pressure occurs the necessary adjustment can be made by means of the screw clip. It is a great advantage to get all the parts of this heat-regulating apparatus fixed on one base, as indicated in the diagram; it can then be carried about from room to room, and can be used at any time without further adjustment.

Details of the Method.

From a burette 23·8 c.c. of acid sodium sulphate solution (No. 1) are run into a conical Erlenmeyer flask of heat-resisting glass. To this the 0·2 c.c. blood obtained as already described are added, and the pipette washed out by alternately sucking in and blowing out the mixture. The flask is corked with a rubber stopper through which a glass tube passes, terminating at its lower end in a capillary point (Fig. 2, A). The flask is heated over a bunsen until a few bubbles appear, indicating that the fluid is approaching the boiling-point. It is then removed from the flame and allowed to stand for 1 to 2 minutes. The stopper is then loosened and withdrawn sufficiently to allow the entry of the point of a pipette containing 1 c.c. of dialysed iron (Solution 2). The iron is added, and the flask corked and well shaken, taking care that any drops of fluid in the neck and upper parts of the flask and on the stopper are washed into the general contents. The flask is then cooled under the tap, and the contents filtered through a 9 cm. Whatman filter paper No. 1. In filtering, all the material must be passed through the filter, since only about 22 c.c. are obtained, and 20 c.c. are required for the estimation. Practically no fluid is lost during the process of coagulation, since the capillary tube permits of the escape of only minimal quantities of steam.

Estimation of Sugar in the Filtrate.

In this estimation it is advisable to use the specially standardised flame described above. For ordinary clinical work quite satisfactory results can be obtained by rough adjustment of the flame, but it is best to have some kind of regulating apparatus between the gas-tap and the burner.

Of the clear filtrate from the deproteinised blood

20 c.c.* are taken and transferred to a small conical 100 c.c. Erlenmeyer flask of hardened glass. It is advisable to use the same flask as has been used for standardising the flame, and to keep this flask for this special purpose. To the flask are added 2 c.c. of the alkaline copper solution (No. 3), which should be very carefully measured. The mixture is then placed over the flame and boiled *in the open flask* for exactly six minutes from the moment at which brisk boiling commences. The flask is then removed, plunged up to its neck into a large volume of cold water in the sink, and kept there for one minute or so, until the contents are quite cold. Thorough cooling is essential.

To the cooled solution 2 c.c. of 25 per cent. sulphuric acid are added, and the flask very gently agitated until the effervescence has passed off. From this point it is allowed to stand for one minute, being shaken with a strong circular motion every few seconds. The N/400 thiosulphate solution is then run in from a burette until the yellow colour almost disappears. Two drops of soluble starch solution are now added; this gives a deep blue colour with the iodine still present. The titration with thiosulphate is continued until this blue colour entirely disappears. The end point is extraordinarily sharp, and there is no difficulty in ascertaining when titration is complete. The number of c.c. of thiosulphate used are noted, and from this the result is calculated.

Calculation of Result.

Supposing the reading on titration is 9·2 c.c. thiosulphate, and that 2 c.c. copper alkaline solution alone require 11 c.c. thiosulphate, the difference (1·8 c.c.) would represent the sugar present in the 20 c.c. of the blood filtrate.

From the table it is seen that 1·8 c.c. thiosulphate represents 0·1 per cent. blood-sugar. The percentages given in this table only hold good when 20 c.c. of the blood filtrate are taken. If any other quantity is used, and this quantity be represented by x c.c., then the correct percentage of sugar is obtained by multiplying the percentage given in the table by $\frac{20}{x}$.

* If the blood is from a diabetic patient and likely to contain much sugar, it is best to take 10 c.c. filtrate and make up to 20 c.c. with acid sodium sulphate.

TABLE V.

GIVING PERCENTAGE OF GLUCOSE EQUIVALENT TO N/400 SODIUM THIOSULPHATE SOLUTION WHEN 20 C.C. BLOOD FILTRATE ARE USED.

N/400 Thiosulphate.	*Percentage of Sugar.*	*N/400 Thiosulphate.*	*Percentage of Sugar.*	*N/400 Thiosulphate.*	*Percentage of Sugar.*
c.c.		c.c.		c.c.	
0·12	0·018	2·22	0·118	4·24	0·218
0·25	0·025	2·35	0·125	4·37	0·225
0·38	0·031	2·44	0·131	4·49	0·231
0·50	0·037	2·61	0·137	4·62	0·237
0·62	0·043	2·74	0·143	4·74	0·243
0·73	0·050	2·86	0·150	4·87	0·250
0·86	0·056	2·99	0·156	4·99	0·256
0·99	0·062	3·11	0·162	5·12	0·262
1·13	0·068	3·24	0·168	5·24	0·268
1·26	0·075	3·36	0·175	5·37	0·275
1·39	0·081	3·49	0·181	5·49	0·281
1·53	0·086	3·61	0·187	5·62	0·287
1·67	0·093	3·74	0·193	5·74	0·293
1·80	0·100	3·87	0·200	5·87	0·300
1·94	0·106	3·99	0·206	5 99	0·306
2·07	0·112	4·12	0·212	6·12	0·312

Summary of Different Steps in Method.

For convenience, the different steps in the estimation of blood-sugar by this method may be summarised as follows:

1. Measure 23·8 c.c. acid sodium sulphate into a flask.
2. Take 0·2 c.c. blood and add it to solution in flask.
3. Heat until boiling commences, withdraw, add 1 c.c. dialysed iron, cool under tap.
4. Filter through starch-free Whatman filter paper.
5. Measure 20 c.c. filtrate into special boiling flask; add 2 c.c. copper iodine solution.
6. Boil mixture over standard flame for 6 minutes after boiling commences.
7. Remove from flame, and cool thoroughly in cold water.

8. Add 2 c.c. 25 per cent. sulphuric acid, and shake gently for some time after effervescence has passed over.
9. Titrate with N/400 thiosulphate, using soluble starch to determine exact end point.
10. Note the number of cubic centimetres thiosulphate required; subtract this from the number of cubic centimetres required to titrate 2 c.c. copper alkaline solution. Look up this number on the table, and read off the percentage.

Some Suggestions for Using the Method in Clinical Work.

When special laboratory facilities are available there is never any difficulty in carrying out the estimation of blood-sugar as above described, and various arrangements for keeping the necessary apparatus may be employed according to individual wishes. Much experience of the method suggests that it is most convenient to have the different solutions in bottles in a small stand consisting of a block of wood as shown in Fig. 4. In the rubber stoppers are fixed pipettes of suitable capacity, which are always ready for use. It is not necessary to close the open ends of these pipettes, though this can be easily done by means of rubber tips. The various solutions and reagents on the stand are:

(1) Sodium sulphate.
(2) Alkaline copper solution.
(3) Dialysed iron.
(4) Sulphuric acid.
(5) Acetic acid.
(6) Starch.

It is best to keep the N/10 sodium thiosulphate solution in a special dark glass bottle. It is preferable to keep this bottle in the dark. A special 5 c.c. pipette should be kept for measuring out the thiosulphate.

When a blood-sugar estimation is to be made, all the pipettes and solutions are at hand. As the same pipettes are constantly being used it is only necessary to return

any pipette to its special bottle after use, and no cleaning is required. During the six minutes of boiling the N/400 thiosulphate solution is made up as already described. The starch solution is also prepared at the same time by taking a pinch of soluble starch in a test tube, and heating it with a small amount of distilled water. The six minutes afford ample time for the preparation of these

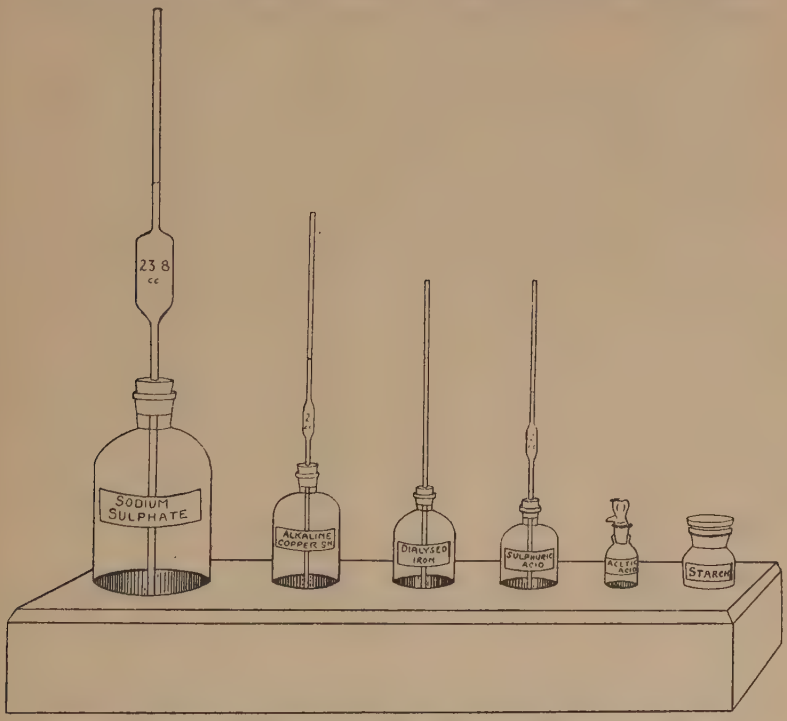

FIG. 4.—METHOD SUGGESTED FOR KEEPING SOLUTIONS AND PIPETTES READY FOR USE.

two solutions. After the boiling of the blood filtrate with alkaline copper solution the mixture is very carefully cooled; on the addition of 25 per cent. sulphuric acid the solution may be titrated at once, for the necessary shaking is done during titration. For ordinary clinical work it is not necessary to have a special regulator for adjusting the gas flame. A flame sufficiently strong to cause

fairly vigorous boiling is all that is necessary. About 4 to 6 c.c. should be left in the flask after the boiling is completed. A very little practice will enable anyone to adjust the flame to the appropriate size. The 20 c.c. pipette used for measuring the filtrate is best kept in a wide-mouthed bottle containing a little glass wool.

CHAPTER VI

THE URINE IN DIABETES AND IN GLYCOSURIA

For the detection of sugar in urine the test most in vogue in this country is Fehling's alkaline cupric tartrate solution. A slightly modified Fehling's solution used for quantitative estimations of sugar by Bertrand's method is described on p. 86, and this mixture is very suitable for qualitative work as well. Since the ordinary solution deteriorates on long standing, it is advisable to keep the copper and the alkaline constituents in separate bottles, and to mix equal parts before using; the resulting solution is used for the test.

When sugar reacts with Fehling's solution, the cupric salt present is reduced to cuprous oxide (Cu_2O). Since this particular combination of copper is insoluble in the alkaline mixture it falls out as a yellow or red precipitate, and its appearance therefore indicates that sugar (or some other reducing substance) is present in the solution tested.

Various suggestions have been made as to the best method for examining urine by means of Fehling's test. After trying many modifications, I am of the opinion that the best and safest way is to take equal parts of the suspected urine and Fehling's solution, and to heat the mixture over the flame in the usual way. Urines in which a distinct reaction is obtained after boiling for a short time may in almost all cases be held to contain a definite amount of sugar, and such urines present no further trouble. Practical experience, however, as well as an examination of the plentiful references to the reaction in the literature, show that the test, as applied to urine in general, is complicated by many difficulties and ambiguities. Different authorities seem to hold

divergent views with regard to the exact significance of certain results obtained with Fehling's test when the reaction is somewhat modified, either with regard to the general appearance of the precipitate or the time taken to produce it. Thus, on testing urine it is sometimes found that no apparent result is evident after a fair amount of heating with Fehling's solution, but that some time after standing an opalescent mixture takes the place of the blue solution, or perhaps there is a fairly definite yellowish-green precipitate. In other cases the mixture of urine and Fehling's solution gives, on boiling for some time, a dirty opalescent, greenish, milky liquid without any sign of a definite precipitate; at other times a more yellowish-green solution is in evidence, and all stages, from a faint dirty greenish opalescence to a definite yellowish mixture exhibiting undoubted evidence of a precipitate, may from time to time be seen. It may be said at once that, in the majority of cases, these ambiguous reactions are evidence of the presence of small amounts of sugar in the urine. Such anomalous results are often very puzzling, but a brief consideration of the way in which they are brought about will make the matter much clearer.

Causation of the Anomalous Reactions.

If we take a normal urine giving no reaction with Fehling's solution, and add to it a trace of sugar, it will generally be found, on subsequent testing in the usual way, that no evidence of the presence of the added sugar can be obtained.

That this is not due to any lack of sensitiveness on the part of Fehling's solution is evident from the fact that this reagent will readily detect such a small quantity of sugar as 1 part in 125,000 parts water (0·8 mgr. in 100 c.c.). Now, since several times this amount of sugar often gives no reaction when added to normal urine and tested with Fehling's solution, we at once arrive at the conclusion that normal urine contains something which prevents

small quantities of sugar giving a reaction with Fehling's solution. This substance is creatinin. Creatinin possesses the power of holding in solution the reduced suboxide, and so the mixture gives no evidence, so far as precipitation is concerned, of the presence of sugar. Now, since *normal urine always contains a small amount of sugar*, every urine would give a reaction with Fehling's test were it not for the creatinin. The normal sugar of urine, of course, reduces its equivalent amount of Fehling's solution in the ordinary way, but since the cuprous oxide formed is held in solution by the creatinin, we get no evidence of the presence of sugar. Thus, when tested with Fehling's solution, average normal urine gives no apparent reaction. Obviously, this action of creatinin is more beneficial than otherwise, for it prevents mistakes being made with urine containing very little sugar—sugar of normal amount and of no pathological importance. The first effect, therefore, of creatinin is to prevent a reaction with small amounts of sugar.

Nature of the Precipitate.

Creatinin, however, possesses another very marked property in that it materially modifies the physical nature of the precipitate when there is a slight excess of sugar present. The different coloured precipitates obtained in urine testing are associated with, and dependent on, a difference in the degree of granularity of the particles of the precipitate. Thus, in a urine giving a dirty greenish opalescent solution, the modified colour is due to the fact that the precipitate of cuprous oxide is present in an exceedingly finely divided state; in the case of a greenish-yellow precipitate, the particles are still very fine, but rather coarser than in the last; with a yellow precipitate they are still somewhat larger, and this increase in the size of the particles goes on until, in a distinct red precipitate, the size of the individual granules is much more marked.

It is customary to state that the red precipitate seen

in testing distinctly diabetic urine is cuprous oxide, whereas the yellow precipitate in evidence when urines containing comparatively small amounts of sugar (say from 1 to 2 per cent.) are tested is cuprous hydrate. This difference in colour, however, is not dependent on the chemical nature of the precipitate present, but on the state of subdivision of the particles, and it is likely that all urines containing sugar really give a precipitate of cuprous oxide, and that the statement to the effect that the yellow precipitate is cuprous hydrate is incorrect. The lower hydrate of copper, $Cu_2(OH)_2$, is such an unstable chemical substance as immediately to suggest a doubt as to whether it is possible for it to exist in urine in the form of a permanent precipitate.

A consideration of the above facts enables us to understand the causation of modified results in urine testing. When the sugar contains just a slight excess of sugar, it reduces its equivalent amount of Fehling's solution in the ordinary way, but the creatinin present modifies the nature of the precipitate, so that it separates out in exceedingly fine particles; these fine particles, floating in the liquid, give a dirty milky greenish appearance to the fluid. It is thus obvious that these ambiguous precipitates are just modifications of the usual form, and are generally indicative of a slight excess of sugar above the physiological amount always present in normal urine. Naturally, the presence of a sufficient amount of some other reducing body such as glycuronic acid would act in the same way, but experiment shows that sugar is really the substance which most often gives these modified reactions.

From the clinical standpoint nothing is to be gained by using too delicate a test when investigating urine for sugar, and such modifications as Benedict's solution possess no advantage over the ordinary Fehling's test. The only point in favour of Benedict's solution is that it keeps exceedingly well, but when Fehling's solution is made up in two solutions as described it also keeps quite well.

The Nature of the Sugars found in Urine.

For practical purposes the only sugars we need consider as likely to be present in urine are pentose, lactose, and glucose. Pentose is seldom found and then nearly always in Jews. The possibility of lactose being the cause of the reduction so frequently given by the urine of pregnant and nursing women is sometimes forgotten. If in the urine of a patient with glycosuria we exclude lactose and pentose, the chances are enormously in favour of the reducing substance being glucose. In case of doubt, the simplest method to ascertain the nature of the sugar is to ferment the urine. This is done by putting a mixture of the urine and baker's yeast into an Einhorn's tube (Fig. 5), and placing it in a warm place either in an incubator at 37° C. or near an open fire for about 1 to 1½ hours. If the yeast is active, the presence of glucose should be definitely established within this time by the appearance of gas at the top of the tube. It is no use leaving the mixture to ferment for 24 hours or so, as is so often recommended in the textbooks. When this is done, bacterial action often sets in, with the result that such a sugar as lactose may be split up into its constituents—galactose and glucose; the glucose then ferments and forms carbon dioxide, thus giving the false impression that glucose was present to begin with. If urine, when fermented with active yeast, gives no result, it may be taken for granted that any fermentable

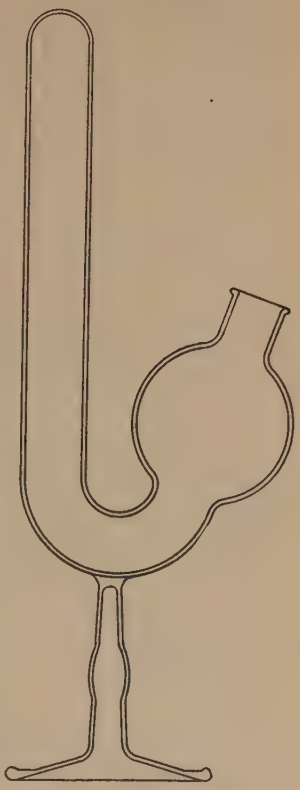

Fig. 5.—Einhorn's Tube.

sugar present is so small in amount as to be of little or no significance.

The use of phenylhydrazine to form osazone crystals is also sometimes of value; generally speaking, if sheaf-like or even short fine clumps of crystals are obtained after heating from anything up to ½ hour, the result is due to glucose. Lactose will also form crystals with phenylhydrazine, but practically they never appear until the mixture has been heated for several hours; they are consequently difficult to obtain in ordinary clinical work.

Pentose may be detected by the use of Bial's test. Details as to these various tests will be found in the ordinary clinical manuals.

The Specific Gravity of the Urine in Diabetes.

Diabetic urine is generally of high specific gravity, owing to the large amount of sugar present, and it is often assumed that a patient whose urine gives a slight or ambiguous reaction with Fehling's solution is more likely to be a diabetic subject if the specific gravity of the urine happens to be high. It must be remembered, however, that high specific gravity of the urine is in no way essentially associated with diabetes, and it is not very unusual to find a urine of specific gravity from 1008 to 1010 containing as much as 1 per cent. glucose. If a very large amount of sugar is present the specific gravity must be high, since each increase of 1 per cent. sugar raises the specific gravity about 4 degrees. In urines with very small amounts of sugar, it is obvious that any high specific gravity present cannot be due to the sugar, since the addition of such a comparatively large amount of sugar as 1 per cent. to a urine of specific gravity 1010 would only raise it to a specific gravity of about 1014. I have had urines giving slight reactions with Fehling's solution from scores of medical men who made the remark that they suspected diabetes, since the slight reaction with Fehling's solution was associated with a high specific

gravity. The fact is that all urines of high specific gravity are likely to give slight reactions with Fehling's test, simply because of concentration, and such highly concentrated urines are much less likely to be diabetic than others giving a slight Fehling's reaction, but of very much lower specific gravity. All urines with a specific gravity over 1025, and giving a slight reaction with Fehling's solution, should be diluted with an equal amount of water and then tested. Frequently, a negative result will be obtained, indicating that the reaction of the undiluted specimen was dependent on high concentration.

A reaction somewhat simulating the sugar reaction with Fehling's solution is sometimes produced by phosphates. This should give no trouble, since the precipitate formed is whitish and flocculent. A flocculent precipitate never indicates sugar.

The Estimation of Sugar in Urine.

Neither Fehling's solution nor any of the many modifications now in use are quite satisfactory for estimating the sugar in urine. In spite of many emphatic statements to the contrary, experience shows that they all suffer from the drawback that the end point in titration is not sufficiently sharp. By far the best procedure for quantitative estimation of sugar is that known as Bertrand's method. Here the end point is exceedingly sharp, and the solutions, with one exception, need not be very accurately made up. It requires but little longer to carry out than any of the ordinary methods, and anyone using it will be unlikely to go back to any other process.

BERTRAND'S METHOD FOR THE ESTIMATION OF SUGAR IN URINE.

The principle here adopted is the same as that of the well-known Fehling's method, but in Bertrand's method use is made of the fact that cuprous oxide, when treated

with a solution of ferric sulphate in sulphuric acid, forms an equivalent amount of ferrous sulphate according to the equation:

$$\underset{\text{(Cuprous Oxide.)}}{Cu_2O} + \underset{\text{(Ferric Sulphate.)}}{Fe_2(SO_4)_3} + H_2SO_4 = 2CuSO_4 + \underset{\text{(Ferrous Sulphate.)}}{2FeSO_4} + H_2O$$

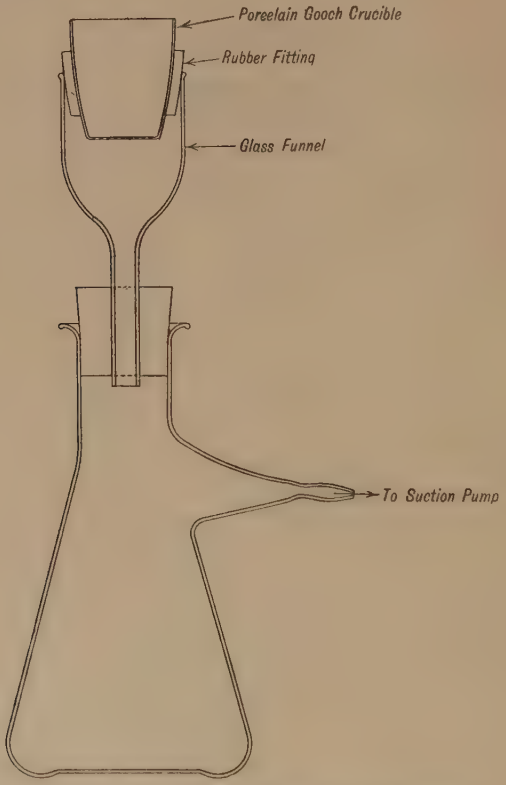

Fig. 6.—Arrangement for Filtration by Suction.

Since this ferrous sulphate decolorises permanganate, the amount present can be ascertained by titrating with standard permanganate. As the amount of permanganate required depends on the amount of ferrous sulphate present, and this in turn depends on the amount of sugar originally present, the amount of sugar in any solution can be ascertained.

The method requires a suction pump and a perforated Gooch crucible fitted for filtering, as shown in Fig. 6. Generally, asbestos is recommended for filtration, but it is more convenient to use a small circle of ordinary good filter paper cut out to fit the bottom of the crucible. Before use the filter paper is put into the crucible and soaked with water, which is then sucked away by means of the pump. This fixes the filter paper in position, and the apparatus is ready for use.

Solutions Required.

Four solutions are required altogether; the first three may be made up roughly, but No. 4 should be prepared as accurately as possible.

No. 1.

Copper sulphate	40 grams.
Water	to 1,000 c.c.

No. 2.

Rochelle salt	200 grams.
Sodium hydroxide	150 „
Water	to 1,000 c.c.

No. 3.

Ferric sulphate	50 grams.
Sulphuric acid	200 „
Water	to 1,000 c.c.

No. 4.

Potassium permanganate ..	5 grams.
Water	to 1,000 c.c.

This permanganate solution must be standardised in order to ascertain how many milligrams of copper, in the form of cuprous sulphate, will decolorise 1 c.c. of it. To do this, one weighs out a small quantity of about 250 milligrams of ammonium oxalate, $(NH_4)_2C_2O_4+H_2O$; the exact amount taken does not matter so long as its weight is

accurately known. This is placed in a beaker, 50 c.c. of water followed by 2 c.c. of concentrated sulphuric acid added, and the mixture warmed to 60° to 80° C. To the warm mixture the permanganate solution is added with constant stirring, until a faint rose pink remains. The number of c.c. required is noted. The number of milligrams of ammonium oxalate taken, multiplied by the factor 0·8951, gives the number of milligrams of copper equivalent to the number of c.c. of permanganate used. From this the value of 1 c.c. of permanganate in terms of copper is estimated and the result put on the bottle. Each c.c. of permanganate should be equivalent to about 10 milligrams copper.

Details for carrying out Method.

The urine to be tested is first examined qualitatively for sugar by Fehling's solution made by mixing equal parts of No. 1 and No. 2 solutions. If a heavy red precipitate is obtained, the urine is diluted twenty times with water (5 c.c. urine + 95 c.c. water); if the precipitate is yellowish, a dilution of ten times is sufficient (10 c.c. urine + 90 c.c. water). To an Erlenmeyer flask of about 150 c.c. capacity 20 c.c. of the diluted urine are transferred by means of an accurately graduated pipette. To this are added 20 c.c. of No. 1 solution and 20 c.c. of No. 2 solution. The mixture is heated over a moderately strong flame for exactly 3 minutes after vigorous boiling commences. The flask is then removed from the flame, and the contents filtered by means of a suction pump through the specially prepared Gooch crucible already described. The flask, which should still contain a good deal of cuprous oxide, is washed out with cold water and the contents passed through the filter as before.

The heavy filtering flask is now disconnected from the Gooch crucible, the contents thrown away, the flask washed with cold water, and the Gooch crucible replaced in the flask. At this point the whole of the cuprous oxide

is either on the filter or in the boiling flask. To the boiling flask is added from 20 to 25 c.c. of the ferric sulphate solution (No. 3), which dissolves the cuprous oxide and oxidises it, being itself reduced to ferrous sulphate. This solution is gradually passed through the filter, so as to dissolve any remaining cuprous oxide on the filter paper and on the sides of the crucible. It is sometimes a little difficult to get all the oxide dissolved, since it tends to adhere closely to the filter, but this can best be done by tapping and pressing the filter paper with a glass rod. Finally, the boiling flask is washed with cold water and the contents again passed through the filter. During the solution of the cuprous oxide it is frequently not necessary to use the suction pump, but it may often be employed with advantage towards the end of the process.

The whole of the cuprous oxide is now in solution in the filtering flask. To this green solution the standard potassium permanganate solution (No. 4) is carefully run in from a burette, with continuous shaking of the flask. A momentary red colour appears, which disappears immediately the permanganate mixes with the solution. More permanganate is added until a faint reddish colour remains. At this point the titration is complete, and the sugar present is calculated by the help of the table.

Calculation.

Supposing 7·2 c.c. permanganate were used and 1 c.c. permanganate=10 milligrams copper, then 7·2 c.c. permanganate=72 milligrams copper, and from the table 72 milligrams copper=37 milligrams glucose. Now if the urine was diluted ten times, 20 c.c. of this mixture (the amount taken for the estimation) would contain 2 c.c. of the original urine.

2 c.c. urine contain 37 milligrams glucose,
∴ 100 c.c. urine contain 1,850 milligrams or 1·85 per cent. glucose.

TABLE VI.

TABLE FOR BERTRAND'S METHOD.

Milligrams Copper.	*Milligrams Glucose.*	*Milligrams Copper.*	*Milligrams Glucose.*	*Milligrams Copper.*	*Milligrams Glucose.*
20·4	10	79·3	41	133·1	72
22·4	11	81·1	42	134·7	73
24·3	12	82·9	43	136·3	74
26·3	13	84·7	44	137·9	75
28·3	14	86·4	45	139·6	76
30·2	15	88·2	46	141·2	77
32·2	16	90·0	47	142·8	78
34·2	17	91·8	48	144·5	79
36·2	18	93·6	49	146·1	80
38·1	19	95·4	50	147·7	81
40·1	20	97·1	51	149·3	82
42·0	21	98·9	52	150·9	83
43·9	22	100·6	53	152·5	84
45·8	23	102·3	54	154·0	85
47·7	24	104·1	55	155·6	86
49·6	25	105·8	56	157·2	87
51·5	26	107·6	57	158·8	88
53·4	27	109·3	58	160·4	89
55·3	28	111·1	59	162·0	90
57·2	29	112·8	60	163·6	91
59·1	30	114·5	61	165·2	92
60·9	31	116·2	62	166·7	93
62·8	32	117·9	63	168·3	94
64·6	33	119·6	64	169·9	95
66·5	34	121·3	65	171·5	96
68·3	35	123·0	66	173·1	97
70·1	36	124·7	67	174·6	98
72·0	37	126·4	68	176·2	99
73·8	38	128·1	69	177·8	100
75·7	39	129·8	70		
77·5	40	131·4	71		

BENEDICT'S METHOD FOR THE ESTIMATION OF SUGAR IN URINE.

Though the method of Bertrand just described is by far the most suitable for sugar estimation when the necessary facilities are at hand, it may not be very convenient for

the general practitioner to carry out this procedure. The estimation of sugar in urine is, however, now of more importance than ever, because of the guidance it affords in the new insulin treatment of diabetes. One of the simplest methods for general use is that of Benedict. Only one solution is necessary, and this solution has the great advantage that it keeps almost indefinitely.

Solution required for Benedict's Method.

Copper sulphate (pure crystals) ..	18 grams.
Sodium carbonate	100 ,,
Sodium citrate	200 ,,
Potassium sulphocyanate	125 ,,
Potassium ferrocyanide (5 per cent. solution)	5 c.c.
Distilled water	to 1,000 c.c.

The carbonate, citrate, and sulphocyanate are dissolved together by means of heat in about 100 c.c. of water, and filtered if necessary. The copper sulphate is very carefully weighed, dissolved in about 100 c.c. of water, and poured slowly into the other solution with constant stirring. After the addition of the ferrocyanide solution the mixture is cooled and made up to 1 litre. With the exception of the copper sulphate, all the ingredients may be weighed out roughly.

25 c.c. Benedict's solution=50 mgrs. glucose.

Method of carrying out Estimation.

Dilute the urine 1 in 10 parts by taking 10 c.c. urine and making up to 100 c.c. in a measuring flask or cylinder. Mix thoroughly. Measure 25 c.c. of Benedict's reagent into an Erlenmeyer flask or porcelain evaporating dish by means of a pipette; add about 10 grams of dry sodium carbonate and a little talc powder. A spoon holding about 10 grams sodium carbonate should be used so as to avoid the necessity for frequent weighing. The mixture is then heated to boiling over a free flame, when the carbonate dissolves. The diluted urine is poured into a 50 c.c.

graduated burette, and from this is slowly run into the boiling alkaline solution. When a chalky white precipitate forms, and the blue colour of the mixture begins to lessen, the diluted urine should be run in drop by drop. When the last trace of blue colour disappears, the number of c.c. of diluted urine required is noted. The solution must be kept boiling throughout the entire titration. With a urine diluted 1 to 10 the calculation is as follows: Let x represent the number of c.c. of diluted urine required to decolorise 25 c.c. copper solution; then

$$\frac{0{\cdot}05}{x} \times 1{,}000 = \text{per cent. sugar in original sample.}$$

This method is very simple, and can be carried out by anyone in a very short time without any special apparatus.

CHAPTER VII

ACIDOSIS AND COMA

DIABETES is associated with the presence of abnormal amounts of acids in the body. Whether this is due to excessive production or diminished oxidation is not definitely known, but inability to destroy the acids as they are formed is probably the dominating feature. These acids are chiefly oxybutyric and diacetic acids; their accumulation in the body gives rise to toxic symptoms, and since the organism is unable to oxidise them in the usual way, it endeavours to excrete them by means of the kidney. The tendency for the development of coma, which is so marked in diabetes, is closely related to this accumulation of large amounts of organic acids in the body, a condition generally referred to as *acidosis*. Now, if we could estimate directly the amount of retained acids in the body, we would be able to forecast, with a fair degree of probability, the chances of coma developing in any given case. Direct estimation is, however, impossible, and so we have to rely for our information on the state of the urine and on certain changes which the acidosis produces in the blood; the extent of these changes indicates, in a general way, the condition of the patient and the likelihood of coma developing.

The more advanced the acidosis, as indicated by the methods described below, the greater is the danger of coma coming on, but it must be understood that the physical changes which acidosis produces, and which are made use of as tests for the condition, are really not the cause of coma. Thus acidosis, for instance, is accompanied by a lowering of the carbon dioxide tension of the alveolar air, but this is not the cause of coma, though both conditions frequently go together. It is possible

to have cases of coma in which many, or perhaps all, of the tests for acidosis give practically normal results, so that a broad view must be taken. Here, as in other pathological states, the clinical condition of the patient must always be most carefully considered, for occasionally this is a better guide than any laboratory test in warning us of the dangers ahead. On the other hand, approaching coma may give little or no clinical evidence of its imminence, and the danger-signal is recognised only when tests are carried out. The nature and value of the tests used in diabetic cases will be best understood when we consider the physical basis of certain results produced by excess of acid in the body.

The Urine in Diabetes.

In severe diabetes the urine always contains a certain amount of acetone, together with oxybutyric acid and diacetic acid, a condition constituting the so-called ketonuria. Frequently, the extent to which these bodies are present affords very important information. Acids are excreted by the body as a rule, not in the form of free acids, but in combination with ammonia as ammonium salts. It has long been held that this neutralisation of acid took place in the liver, but in a recent communication by Benedict evidence is brought forward that this is probably a function of the kidney. The kidney breaks down urea to form ammonia, and this ammonia combines with the acid to form a salt. By this means, no doubt, the body prevents the loss of large amounts of the more valuable bases such as sodium, for it is probable that the acid is brought to the kidney largely in the form of a sodium salt; the kidney retains the sodium, and replaces it by ammonium derived from the plentiful urea. At any rate, the result is that the presence of large amounts of acid in the body is usually indicated by the presence of a large amount of ammonium salt in the urine. This so-called "free ammonia" can

be easily estimated, and provides a fairly reliable index of the extent of the acidosis. Sometimes, however, excessive amounts of acid may be present in the body, but the kidney may fail to excrete them, and in such cases the urinary ammonia gives no clue to the true state of affairs. On the whole, it is found practically that the amount of free ammonia present in the urine is a very good guide as to the patient's condition. Since a certain amount of the acids present in diabetes are excreted as free acids, the extent to which the acidity of the urine is raised above the normal also affords us a good deal of information.

The Ammonia Coefficient.

Normally, a small amount of the total nitrogen of urine exists in the form of ammonium salts. The relation which the nitrogen of this free ammonia bears to the total nitrogen of the urine is known as the "ammonia coefficient," and under normal circumstances in the healthy subject this amounts to 1:20 or so. In severe diabetes the relationship may change to 1:2 or even more, in consequence of the excessive amount of ammonium salt present. Though largely influenced by diet, and especially by the ingestion of sodium bicarbonate, this coefficient is frequently of great value.

Other methods available for the investigation of diabetic patients comprise such procedures as the following:

1. **Determination of changes in blood reaction.**
2. **Estimation of the dissolved carbonic acid of the blood.**
3. **Estimation of the sodium bicarbonate of the blood.**
4. **Estimation of carbon dioxide in the alveolar air.**

To understand the significance of these investigations, it is necessary to consider shortly certain changes which excess of acid in the body brings about in the blood. It may be said at once that little evidence of acidosis

is found by investigating the reaction of the blood, for, unlike ordinary liquids such as water, the blood reaction does not change even after the addition of comparatively large amounts of acid. This power of the blood to retain its normal reaction at a constant level is associated with a somewhat complex mechanism in which such substances as carbonic acid, carbonates, phosphates, and proteins all play a part. The efficiency of this mechanism is chiefly dependent on the relative amounts of dissolved carbon dioxide and sodium bicarbonate present in the blood. If we dissolve a weakly acid substance like carbon dioxide in water, and add a little sodium bicarbonate, which acts as a weak base, the solution will have a definite reaction, depending on the relative amounts of the two substances present. Within certain limits, the reaction is the same whatever *total amount* of these substances is present. What does matter is that the amount of *carbonic acid should always bear the same relationship to the amount of sodium bicarbonate;* as long as this relationship is maintained the reaction remains constant. Now the blood contains a system, $\frac{H_2CO_3}{NaHCO_3}$, in which, normally, the carbon dioxide, dissolved as carbonic acid, represents about one-twentieth the amount of CO_2 present as bicarbonate. This relationship is maintained with extraordinary consistency, for whenever a little too much carbonic acid is present, the slight temporary increase in carbonic acid reacts on the respiratory centre, with the result that the excess of carbonic acid is thrown out by increased ventilation of the lungs. Any tendency to excess of sodium bicarbonate is also dealt with in various ways. The addition of acid to the blood causes a reduction of the sodium bicarbonate, since some of the acid combines with this substance. This results in a temporary increase of carbonic acid, which is dealt with as before, so as to maintain the necessary constant relationship between the carbonic acid and the carbonate. The blood now contains the same *relative* amounts of these substances, but

the *total* amount of both is diminished. The effect of adding acid to the blood is therefore to reduce both the amount of carbonic acid in solution and the amount of bicarbonate present; the extent to which these bodies are reduced indicates the extent of the acidosis. Since, however, the amount of carbon dioxide in the alveolar air depends directly on the amount in the blood, the alveolar air of a patient with a low carbonic acid content in the blood will contain less carbon dioxide than is present in normal alveolar air. Thus, excess of acid in the body results in a decrease of sodium bicarbonate and carbonic acid in the blood, and a consequent lessening of the carbon dioxide in the alveolar air. Methods by which these changes can be estimated are described below.

THE SIMPLER METHODS IN USE FOR INVESTIGATING DIABETES.

Many of the methods suggested for use in the management of a case of diabetes are much too elaborate for general use, and only the simpler methods which can be employed by any medical man are described here. When patients are free from ketonuria, as indicated by the usual acetone and diacetic acid tests, there is no risk of coma developing, and no special tests are necessary. In bad cases of diabetes, coma is always looming in the distance, and may at any time quickly supervene, so that it is essential that we should possess some means whereby indications of its probable onset may be obtained. As already stated, no single test is of much value *per se*, but it is nearly always possible by means of a few comparatively simple procedures to get all the information necessary in any given case. The results of these tests, when considered in relation to the clinical condition, will generally enable us to steer clear of the many rocks with which the treatment of diabetes is strewn. The examination of the urine for sugar and ketone bodies is essential

in all cases. For ketosis the following well-known tests are the best:

Rothera's Test for Acetone.—Take about 2 inches of urine in a test-tube and saturate it by shaking with finely ground ammonium sulphate crystals. To the solution add a few drops of a recently prepared 10 per cent. sodium nitroprusside solution and about as much ammonium hydrate as the amount of urine taken. Shake up. The production of a permanganate colour in the fluid indicates the presence of ketone bodies. Though this is generally spoken of as a test for acetone, it gives a reaction with diacetic acid as well; indeed, the test is a much more sensitive one for diacetic acid than for acetone, and it is now known that the chief cause of the reaction obtained in diabetic urine is really diacetic acid.

Gerhardt's Test for Diacetic Acid.—This test is carried out by adding a few drops of 10 per cent. ferric chloride solution to some of the urine in a test-tube. Frequently, a precipitate of ferric phosphate occurs and somewhat obscures the reaction, but this can be filtered off if necessary. Ferric chloride is added to the urine, drop by drop, until a precipitate ceases to form. The production of a port wine or claret colour indicates the presence of diacetic acid. It is generally quite unnecessary to filter, as the particular colour is easily observed, even in the presence of considerable amounts of ferric phosphate.

These two tests are frequently used in diabetic cases on the assumption that Rothera's test indicates the presence of acetone, and ferric chloride the presence of diacetic acid. Since experience shows that a reaction with ferric chloride generally indicates a more severe condition, it is customary to state that the presence of diacetic acid is a more grave sign than the presence of acetone alone. The true explanation of the position is that diabetic urines reacting with Rothera's test all contain diacetic acid, and generally in very much greater

amount than acetone. When diacetic acid is present in comparatively large amounts it gives a reaction with ferric chloride, but small amounts of diacetic acid give no reaction with this substance. Hence a positive Gerhardt's reaction merely indicates that the diacetic acid has largely increased in amount; it really acts as a kind of quantitative method. Naturally, the greater the amount of diacetic acid present, the more serious the condition, and so a positive ferric chloride reaction is of more importance than one with nitroprusside. By carrying out both reactions in each patient a good idea of the extent of the ketonuria is obtained.

Total Acidity of Urine.

Estimation of the total acidity of the urine is a very simple process, and may be of value in the case of some patients, since it is known that free oxybutyric acid may sometimes be excreted in diabetes. Any marked increase in total urinary acidity in these patients would be suggestive of the presence of excessive amounts of acid in the organism.

Folin's Method for Estimating Acidity of Urine.—Measure 25 c.c. of the urine into a small flask and dilute with about 100 c.c. of water. Add about 15 grams of finely powdered potassium oxalate and 6 drops of phenolphthalein solution (1 per cent.), and shake for one minute. Then run in N/10 sodium hydroxide from a burette until the solution has a permanent and distinct though slight pink colour. The result is expressed in terms of the number of cubic centimetres of N/10 hydroxide required either per 100 c.c. urine, or per 24 hours quantity. Most estimations run between 20 and 40 c.c. of decinormal solution per 100 c.c. urine. According to Folin, the normal acidity of the 24 hours output may be placed at 550 to 670 c.c. of decinormal solution, but many authors quote much lower results.

"Free Ammonia" in Diabetic Urine.

The estimation of free ammonia is easily carried out by the use of formalin, and though the results are not absolutely correct they are quite satisfactory for clinical purposes. This estimation depends on an observation made by Malfatti that when a neutral solution of an ammonium salt is treated with formaldehyde, a reaction occurs, with the result that urotropin is formed and a corresponding amount of acid liberated, according to the equation:

$$4NH_4Cl + 6CH_2O = N_4(CH_2)_6 + 6H_2O + 4HCl.$$
(Formaldehyde.) (Urotropin.)

The amount of acid liberated is determined by titration with standard alkali.

Estimation of Ammonia.—25 c.c. urine are neutralised with N/10 sodium hydroxide exactly as described above for the estimation of acidity. To this are added 10 c.c. formalin diluted with 2 volumes of water and neutralised by means of sodium hydroxide, using phenolphthalein as an indicator. The pink colour of the urine disappears owing to the acid liberated. Run in N/10 sodium hydroxide from a burette until a slight permanent pink colour is again obtained. Note the number of cubic centimetres alkali required, and from this calculate the ammonia.

1 c.c. N/10 sodium hydrate = 0·0017 gram ammonia or 0·0014 gram nitrogen.

Generally, the output of ammonia should not exceed more than about 1 gram per day, or somewhat less, so that 100 c.c. urine should not contain more than about 0·05 to 0·1 gram. Larger amounts than this should be considered pathological. In bad cases of diabetes the ammonia output may amount to several grams per day, indicating a considerable excretion of acid. The higher the ammonia the more serious the condition, but exceptions occasionally arise. The amount of ammonia

excreted is to some extent dependent on diet, and during alkali therapy it may be small even when marked acidosis is present.

AMMONIA COEFFICIENT IN DIABETES.

The relation of the urinary ammonia to the total nitrogen—*i.e.*, $\frac{\text{nitrogen as ammonia}}{\text{total nitrogen}}$, or the so-called ammonia coefficient—sometimes gives a good deal of information in indicating the extent of acidosis. As already stated, this coefficient in normal urine usually lies in the region of $\frac{1}{20}$, and any marked change is of importance. In the case of diabetic patients on a fair diet, a coefficient as high as $\frac{1}{3}$ or $\frac{1}{4}$ frequently indicates, in my experience, a hopeless prognosis. Sometimes a coefficient approaching to the normal may be found in the urine of patients taking alkali, and yet their condition may be very serious. Indeed, it may be said that the use of alkali for therapeutical purposes renders these ammonia tests more or less valueless. Low coefficients are obtained in many other pathological conditions, but in such cases they do not bear the same grave significance as they do in diabetes.

Estimation of Total Nitrogen in Urine.

Unfortunately the estimation of the total nitrogen of the urine by the ordinary Kjeldahl method, though a simple enough process, cannot be carried out without a fairly well-equipped laboratory. For practical purposes, however, a sufficiently accurate result may be obtained by the use of hypobromite. A small quantity of urine is treated with alkaline hypobromite, and the amount of nitrogen evolved carefully measured by means of one of the various pieces of apparatus used in urea determinations.* For practical purposes we may assume that

* A simple process is fully described in the author's monograph "Modern Methods in the Diagnosis and Treatment of Renal Disease," Constable and Co., 1921.

each cubic centimetre of nitrogen evolved represents 0·0014 gram nitrogen in the urine.* From this the total nitrogen in 100 c.c. urine is easily calculated.

The following example is taken from an actual case of severe diabetes; patient was on a moderate diet chiefly consisting of protein with some fat.

25 c.c. urine after neutralisation and the addition of formalin required for neutralisation 80 c.c. N/10 alkali. Now 1 c.c. N/10 alkali = 0·0014 gram nitrogen; therefore 25 c.c. urine contained $80 \times 0{\cdot}0014 = 0{\cdot}1120$ gram nitrogen, and 100 c.c. contained 0·4480 gram nitrogen as ammonia.

4 c.c. of this urine, when treated with alkaline sodium hypobromite solution, evolved 30 c.c. nitrogen. Now 1 c.c. nitrogen gas = 0·0014 gram nitrogen; therefore 4 c.c. urine contained $30 \times 0{\cdot}0014 = 0{\cdot}042$ gram nitrogen, and 100 c.c. urine contained 1·05 gram, total nitrogen.

$$\text{Now } \frac{\text{ammonia nitrogen}}{\text{total nitrogen}} = \frac{0{\cdot}4480}{1{\cdot}05} = \frac{1}{2{\cdot}4} \text{ ammonia coefficient.}$$

By these simple methods of estimating the ammonia and total nitrogen approximately accurate results can be obtained in a few minutes. Both methods, of course, are open to objections, and neither of them gives quite accurate results, but for practical clinical purposes it is questionable whether they are not quite as useful, and capable of giving as much information as the more exact methods. Theoretically, specimens of the carefully preserved output of 24 hours should be used, and when obtainable they should be taken for the estimations, but experience shows that quite useful information is given by freshly passed specimens. One disadvantage in using a specimen of the 24-hour output is the difficulty of preventing decomposition in the urine when it is kept. It may

* The weight of 1 c.c. nitrogen at normal temperature and pressure is 0·001258 gram, but since all the urinary N is not evolved, it is best, for the purpose of this estimation, to assume that 1 c.c. N = 0·0014 gram.

safely be said that many of the high ammonia contents so frequently found in specimens from the total daily excretion depend largely on ammonia produced from urea by bacterial action after the urine was passed. A specimen obtained immediately before examination will give all the information yielded by a 24-hour specimen, and the results will certainly be more reliable in the majority of cases. Again, in patients threatening coma, it may be impossible to wait for the collection of a 24-hour specimen.

The most accurate and scientific method for the estimation of ammonia is one in which the urine is treated with excess of potassium carbonate and the liberated ammonia aerated through a standard acid solution by the help of a suction pump. For estimation of total nitrogen the only accurate method is Kjeldahl's process. For exact scientific observations these methods should be used, but for clinical work they are superfluous, since the processes described are found to be quite satisfactory in the great majority of cases.

Carbon Dioxide Content of the Alveolar Air.

Under ordinary conditions the normal average percentage of carbon dioxide in alveolar air is about 5·5 per cent. in men, while in women and children it is about 5 per cent. Generally, the amount present is dependent on the amount in the blood, so that reduction in blood carbonic acid resulting from acidosis is reflected in the alveolar air. Sometimes, however, the carbon dioxide content is lowered by factors other than blood changes associated with acidosis, and in such cases estimation of the alveolar carbon dioxide may give quite wrong impressions. Excessive lung ventilation, as illustrated by the effects of high altitudes, will lower the carbon dioxide of the alveolar air, and it is obvious that the same effect may be produced by any condition, either in the heart or lungs, which interferes with the exchange of gases between the blood and the alveolar air. In spite of these

drawbacks, examination of the alveolar air provides an excellent and generally reliable means for ascertaining the condition of a diabetic patient. According to Poulton, a value of 2 per cent. carbon dioxide in the alveolar air indicates the onset of coma within 24 hours, while a value of 3 to 4 per cent., though much less dangerous, suggests the probability of coma coming on within 3 or 4 days. It must be stated that the estimation of alveolar carbon dioxide gives most reliable information, on the whole, when the results are distinctly low. With moderately high values the danger of coma does not seem to be so great as might be expected, and sometimes indications by other tests suggest that the moderate values occasionally found do not really bear the grave significance which is usually attached to them. There are various methods for estimating alveolar carbon dioxide, but the simplest and best, from the clinical point of view, is that devised by Fridericia. This method is so exceedingly simple that it can be carried out by anybody in a very short time; it has the further advantage that the whole procedure can be performed at the bedside without the use of any apparatus other than that suggested by Fridericia.

Fridericia's Method for Estimation of Alveolar Carbon Dioxide.

A very full description of the apparatus used is given by Poulton.* As shown in Fig. 7, it consists of two limbs, A and B, bent in the form of a U-tube. At the bottom of the U-tube is a three-way tap, C, which connects the two limbs, A and B, with each other, or either of them with the outer air through the tube Z. At the top of the A limb is a mouth-piece, K, and a little lower an ordinary two-way tap, L. The total volume of A between L and C must be accurately measured, and the scale graduated in percentages of this volume up to 7 per cent.

* *British Medical Journal*, 1915, 2, 393.

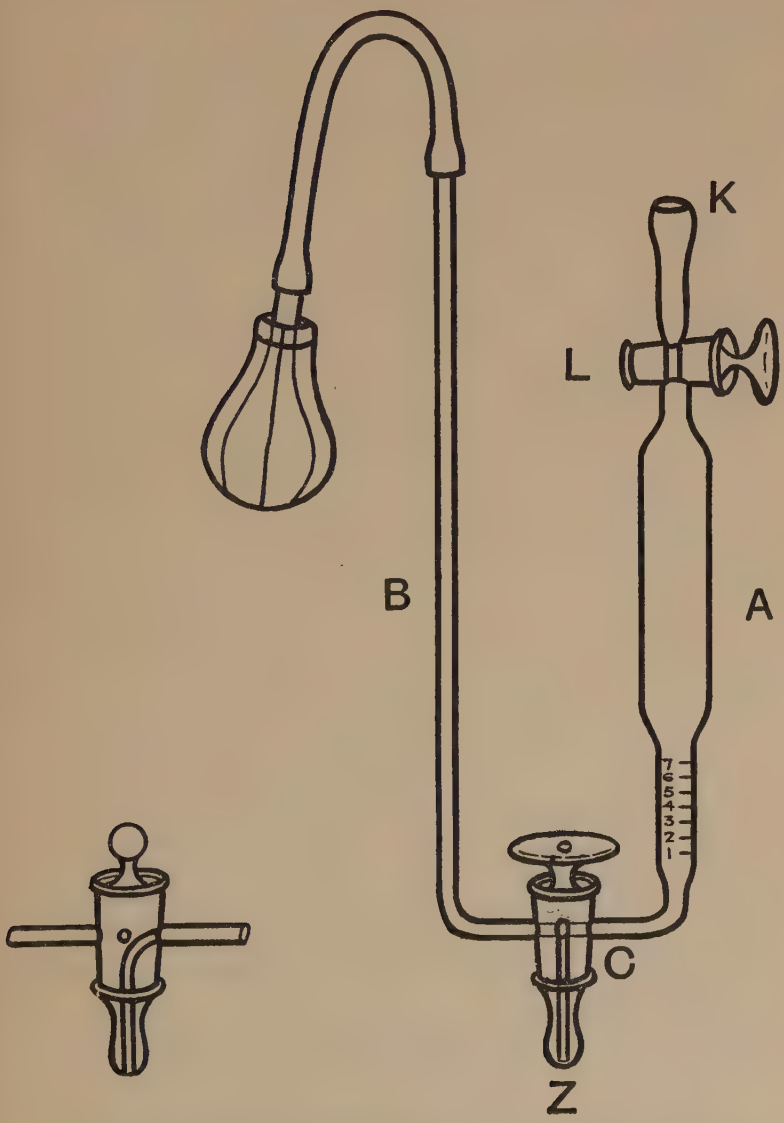

FIG. 7.—FRIDERICIA'S APPARATUS FOR ESTIMATING CO_2 IN ALVEOLAR AIR.

Before carrying out an estimation tap L must be opened, and tap C put in the position in which A and B communicate.

To carry out an investigation, the patient takes a normal inspiration and puts the mouth-piece in his mouth. He then blows as *hard and as quickly as possible* through the apparatus.* Care must be taken not to take a deep breath before exhaling, and to keep the breathing as normal as possible immediately prior to the taking of the sample.† The apparatus is now filled with alveolar air, and the operator closes tap L, but leaves tap C unchanged. The whole apparatus, which is weighted by means of a wooden frame, is now put into a water-bath at room temperature and left there for 5 minutes. On cooling, the air volume decreases, and some alveolar air from B is drawn into A, but there is no risk that the atmospheric air drawn into the top of B should reach A, nor does diffusion play any appreciable part. Tube A now contains alveolar air at the temperature of the water-bath.

The next step in the process is to ascertain the amount of carbon dioxide in this alveolar air under similar conditions of temperature and pressure. To do this, tap C is turned so as to close A and connect B with the outlet Z. By means of suction with a rubber bulb at the top of B, about 2 or 3 c.c. of 20 per cent. sodium hydroxide are drawn through Z into limb B. Tap C is then turned so that A and B communicate once again, and the soda forced, by means of slight pressure, into A, tap L being kept closed. During this manipulation limb B is depressed slightly so as to prevent the escape of any alveolar air through tap C.

The third step consists in closing A by turning the tap C so that B is connected with the outlet, and any soda

* The rubber bulb shown in the diagram is, of course, not attached at this stage.

† For various other methods of obtaining alveolar air see Boothby and Peabody, *Arch. Int. Med.*, 1914, 13, 497.

remaining in B is allowed to run out. The apparatus is inverted a few times with gentle shaking for half a minute or so to effect the absorption of the carbon dioxide by the caustic soda. The apparatus is then returned to the water-bath, and the stopcock C turned, with the tap under water, so that A communicates with the water through outlet Z. After 5 minutes the instrument is carefully raised till the water stands at the same level in A and in the water-bath. By this operation the gas in A is brought to the same conditions of temperature and pressure as before the absorption of the carbon dioxide. The reading of the meniscus of the fluid in the graduated tube represents the percentage of carbon dioxide in the sample of air taken. These figures can be changed into millimetres of mercury, if desired, by multiplying the barometric pressure by the percentage found and dividing by 100. The apparatus should be thoroughly cleaned and washed out with a little dilute acid before use, since even traces of alkali will interfere with the accuracy of the method by absorbing CO_2.

Sodium Bicarbonate Content of the Blood in Diabetes.

Van Slyke and his colleagues have brought forward a good deal of evidence pointing to the conclusion that one of the best indications of acidosis is to be found in the amount of sodium bicarbonate in the blood or plasma. Though it is easy enough to estimate the sodium bicarbonate in whole blood, it is much more convenient, from the technical point of view, to use plasma, and this is generally done. When estimated by the Van Slyke method described below, it is found that the plasma of the normal resting man contains on an average about 65 c.c. CO_2 bound as bicarbonate per 100 c.c. plasma measured at 0° C. and 760 mm. pressure. In bad diabetes the figure is much less, and the method is a most sensitive indicator of the severity of the acidosis and the likelihood of coma supervening.

As an indication of the results obtained in diabetes, the following figures are given by Van Slyke:

Normal resting adult; extreme limits	53 to 77 per cent.
Mild acidosis; no visible symptoms ..	40 to 53 ,,
Moderate acidosis; symptoms may be apparent	30 to 40 ,,
Severe acidosis; symptoms of acid intoxication	Below 30 ,,
Lowest CO_2 observed with recovery ..	16 per cent.

Though the results are very useful in diabetes they cannot be relied on absolutely, for sometimes low bicarbonate values are present without any signs of coma. The method should be used in conjunction with other tests. It is very easy to carry out when all the necessary preparations are made beforehand; indeed, the actual determination itself does not take more than a few minutes. Certain theoretical points connected with the method require a rather complex explanation, but the practical application of the procedure is simple. For complete details the original paper should be read.*

VAN SLYKE'S METHOD FOR DETERMINING SODIUM BICARBONATE IN PLASMA.

The method is best described under four headings as follows:

1. **Taking of blood sample.**
2. **Separation of plasma.**
3. **Saturation of plasma.**
4. **Actual determination of bicarbonate.**

1. Taking of Blood Sample.

For at least an hour before the blood is drawn the patient should be at rest. The blood is taken from an arm vein directly into a centrifuge tube containing enough powdered potassium oxalate to make about 0·5 per cent. of the weight of the blood drawn. It is desirable to avoid

* *Journ. Biol. Chem.*, 1917, **30**, 347.

stasis as much as possible, but even in cases in which stasis has to be maintained for some little time, fairly good results are obtained. If possible, however, it is best to relax the

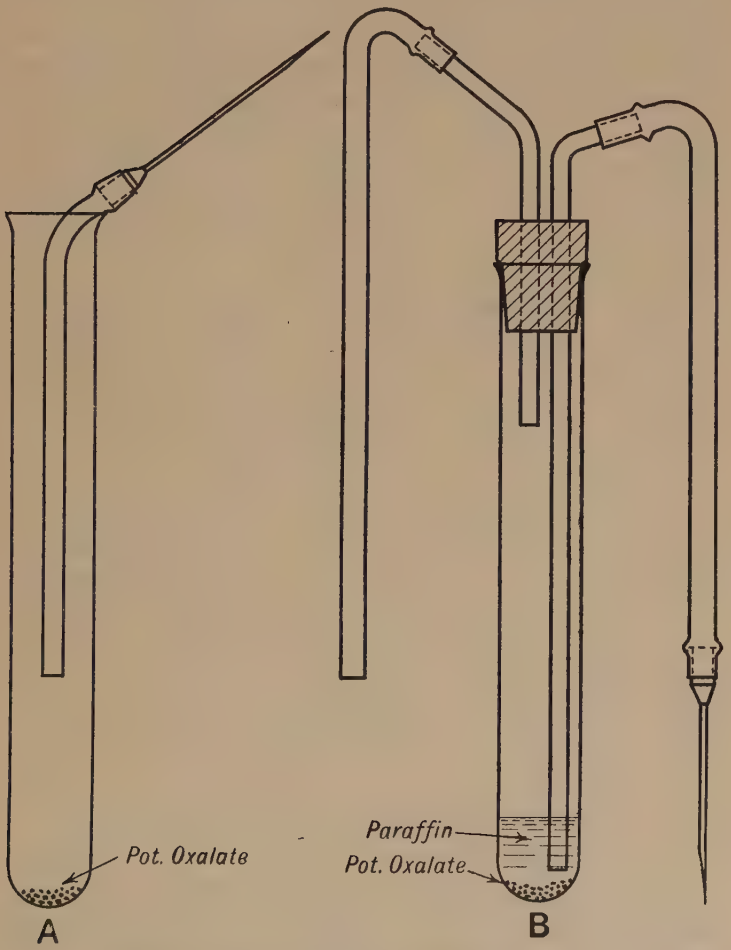

FIG. 8.—NEEDLE ARRANGEMENTS FOR DRAWING BLOOD FROM A VEIN.

ligature as soon as the vein is entered, and allow a few seconds for the stagnant blood to pass. The blood can be taken by an ordinary needle with a piece of rubber attached (Fig. 8, A). After taking the blood the tube is

turned on its side and back to the vertical position once or twice after the sample has been drawn, in order to mix the oxalate. A tube fitted up as in Fig. 8, B, may also be used for drawing blood. Here the blood is collected and centrifuged under paraffin oil. The slight amount of agitation necessary in order to assure admixture of the oxalate is accomplished by stirring with the inlet tube, and the tube must be submitted to the minimum of agitation after the blood is in it. If the specimen is obtained by means of a syringe, no appreciable suction must be applied.

2. Separation of the Plasma.

If a centrifuge is available, it is best to separate the plasma by centrifuging as soon as possible after the blood is drawn, but quite good results can be obtained by allowing the blood to stand until sedimentation of the corpuscles takes place. When this plan is used, the tube should be completely filled with blood and corked so as to prevent the escape of any CO_2. The plasma should be drawn off as soon as possible. Sterile plasma can be preserved for several days without alteration in its CO_2 capacity, if kept cold and in tubes that have been paraffined in order to avoid solution of alkali from the glass. In ordinary glass, plasma can be kept only for a few hours.

3. Saturation of Plasma with Air containing CO_2 under Normal Alveolar Tension.

It has been definitely shown by various observers that the actual amount of sodium bicarbonate present in plasma at any given time is influenced by the amount of CO_2 in solution. It is therefore obvious that the best results would be obtained when the plasma contains the same amount of dissolved CO_2 as it did when circulating in the arterial blood. This ideal condition is rather difficult to attain *in vitro*, but quite satisfactory results

can be obtained by saturating the plasma with air containing carbon dioxide under normal alveolar tension. For practical purposes alveolar air, which normally contains about 5·5 per cent. CO_2, can be used. Saturation is brought about by means of the arrangement seen in Fig. 9. K is a separating funnel of about 300 c.c. capacity attached by a rubber tube to a bottle, B, filled with glass beads. The glass beads are used to condense the excess of moisture in the alveolar air, which would otherwise dilute the plasma. The plasma is placed in the funnel, and the operator, without inspiring more deeply than normal, expires as quickly and as completely as possible through the bottle of glass beads and the separating funnel connected. The stopper is inserted just before

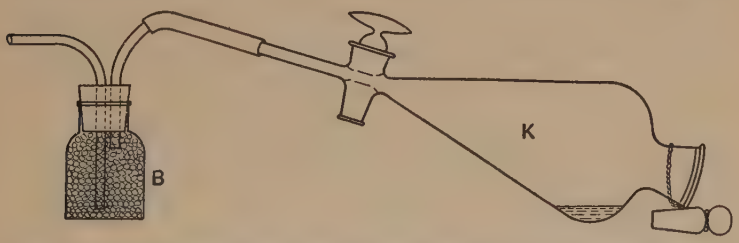

FIG. 9.—ARRANGEMENT FOR SATURATING PLASMA WITH CO_2 AT ORDINARY ALVEOLAR TENSION.

the expiration is finished, so that no air can be drawn back into the funnel. The tap is now closed, and the funnel turned end over end for about 2 minutes, the plasma being distributed, in as thin a layer as possible, completely over the interior of the funnel.

After saturation is completed, the funnel is placed upwards and allowed to stand for a few minutes until the fluid has drained from the walls and gathered in the contracted space at the bottom of the funnel. A sample of 1 c.c. is drawn with a graduated pipette, and used for the determination as described below. If the plasma is scarce, 0·5 c.c. will suffice; in this case the volume of distilled water and acid used to wash the plasma into the apparatus (see below) is also halved, so that the total

volume of water solution introduced is only 1·25 c.c. The volume of gas observed is multiplied by 2, and from this the volume of chemically bound CO_2 calculated.

4. Determination.

The apparatus used is shown in Fig. 10. It is fixed in a clamp, from which it can easily be removed when required. The cocks should be held in place by means of rubber bands. Before a determination is made, the entire apparatus, including the capillaries above the upper cock E, is filled with mercury. To test the apparatus for tightness and freedom from gases the mercury bulb M is lowered until the mercury falls to about the middle of D. The bulb is then again raised. If the apparatus is tight and gas free, the mercury will refill the pipette completely and strike the upper cock with a sharp click. If there is any gas in the apparatus, it acts as a cushion, and the click is not heard; on examination, a bubble of gas will be found above the mercury. If this is the case, the apparatus must be repeatedly evacuated until all the gas has been removed.

Dropping bottles with pipettes and containing the following solutions should be prepared beforehand:

1. Distilled water.
2. Caprylic alcohol.
3. Approximately 5 per cent. sulphuric acid.
4. Mercury.
5. 1 per cent. ammonium hydrate (carbonate free).

To prepare No. 5 solution, add a small amount of saturated barium hydrate solution to ordinary ammonia. The barium carbonate formed is filtered off, and any excess of barium remaining, precipitated by a little ammonium sulphate.

In carrying out an actual determination the apparatus, including both capillaries above the upper cock, is filled with mercury, and the cup P at the top washed free of acid with carbonate-free ammonia: 1 c.c. of plasma

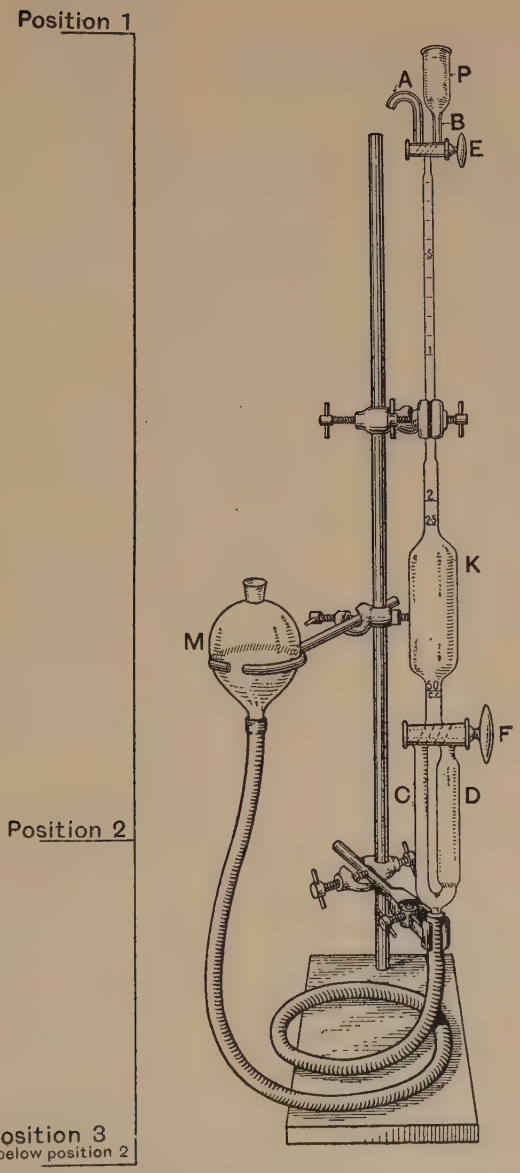

FIG. 10.—VAN SLYKE'S APPARATUS FOR ESTIMATING BICARBONATE IN BLOOD.

is then run into this cup from a pipette, taking care that the point of the pipette dips below the surface of the solution in the cup during the transfer. If necessary, smaller or larger amounts of plasma may be used. With the mercury bulb in position 2, and cock F in such a position that chamber K communicates with D, the solution is admitted from the cup into the 50 c.c. pipette chamber K, leaving just enough above the cock to fill the capillary (B). The cup is washed twice into the pipette with about 0·5 c.c. water each time. A very small drop of caprylic alcohol is now added to prevent frothing, and then 0·5 c.c. sulphuric acid. The exact amount of water and acid added does not greatly matter, but the total volume of the liquid introduced must extend exactly to the 2·5 c.c. mark on the apparatus. As each portion of water is added, enough is left above the cock to fill the capillary, so that no air can enter the latter with the next solution that is added. After adding the acid, a drop of mercury is placed in B and allowed to run down the capillary as far as the cock in order to seal the latter. Any sulphuric acid that remains in the cup is washed out with a little water.

The mercury bulb is now lowered to position 3, and the mercury in the pipette is allowed to run down to the 50 c.c. mark, producing a vacuum in the apparatus. When the *mercury* meniscus has fallen to the 50 c.c. mark, the lower cock F is closed. The apparatus is now removed from the clamp and turned upside down fifteen or more times, so as to agitate its contents thoroughly. By this means the greater part of the CO_2 is extracted from the fluid, and remains in the chamber. The pipette is then returned to the clamp.

By turning the lower cock F the water solution is now allowed to flow from the pipette completely into D without allowing any of the gas to follow it. The mercury bulb is then raised in the left hand, while with the right the cock is turned so as to connect the pipette K with C. The mercury flowing in from C fills the body of the

pipette, and as much of the graduated stem at the top as is not occupied by the gas extracted from the solution. A few hundredths of a c.c. of water floats on top of the mercury in the pipette, but the error caused by reabsorption of carbon dioxide into this small volume of water is negligible if the reading be made at once. The mercury bulb is now adjusted so that the level of the mercury in the burette is the same as that in the mercury bulb. The volume of gas above the water is then read off. The results are expressed in terms of the number of cubic centimetres of CO_2 chemically bound as $NaHCO_3$ in 100 c.c. of the plasma. The calculation is done by means of tables furnished by Van Slyke, but sufficiently accurate results can be obtained by taking the reading on the burette and subtracting 0·12. The result expresses the fraction of a cubic centimetre of carbon dioxide in 1 c.c. plasma. By omitting the decimal point, the figures obtained indicate directly the volume of CO_2 per 100 c.c. of plasma.

Thus, for example, if the reading on the apparatus is 0·76, we subtract 0·12, leaving 0·64, which represents the percentage of carbon dioxide bound by 1 c.c. of plasma. For 100 c.c. of plasma multiply 0·64 by 100; this gives 64 per cent., which is about the normal figure.

SELLARD'S TEST FOR ACIDOSIS.

Of all the tests used for estimating acidosis, by far the simplest is that devised by Sellard. Though of little value in nephritic cases, it is often very useful in diabetes.

The principle of the test depends on the fact that a normal individual will secrete an alkaline urine after taking from 5 to 10 grams of sodium bicarbonate. When acidosis is present, the excess of acids in the body combines with the alkali and forms a neutral salt, so that much more alkali has to be given before the urine becomes alkaline. In very bad cases it may be almost impossible

to get an alkaline urine even after the administration of very large doses of alkali. In moderate cases 30 to 60 grams will suffice. A fair conception of the severity of the condition can often be obtained by means of the test. If the urine is easily rendered alkaline by small amounts of alkali, the onset of coma need not be feared. In carrying out the test, the urine is examined 1 hour or so after the ingestion of successive 5 gram doses of sodium bicarbonate until an alkaline reaction is obtained. The different specimens of urine should be boiled, and on cooling, tested with litmus paper.

CHAPTER VIII

THE MODERN DIETETIC TREATMENT OF DIABETES

Dietetic treatment of diabetes, while formerly the sheet anchor of our hopes, is now *per se* only of secondary importance, though still very essential. When a patient fails to respond to dietetic treatment he is now given insulin, his diet and insulin dosage being carefully correlated.

Since, however, every patient should be tried with dietetic treatment before deciding to use insulin, a knowledge of the principles of dietetic therapy is as necessary as ever, particularly in view of the fact that insulin may prove useless unless carefully correlated with diet.

Attempts at Dietetic Treatment of Diabetes.

For a very long time attempts have been made to treat diabetes by modifications of the diet. Since the most obvious symptom of diabetes is the presence of large amounts of sugar in the urine, the natural inference was to limit the carbohydrate in the food, and this was the basis on which treatment had hitherto been founded. The older observers, however, had no very definite conception of the underlying defects in diabetes, and in the light of present views it is somewhat amusing and interesting to read accounts of the many controversies that were fought out as to the good or bad effects of certain perfectly empirical dietetic measures. Up to quite recent times it was customary to limit the carbohydrate, and to replace this by protein and especially by fat; indeed, quite excessive amounts of fat were frequently given, forgetful of the fact that fat is the principal

agent in producing ketonuria and acidosis. Gradually, it began to dawn upon investigators that the older principles of treatment were unsatisfactory, and within the last ten years a good deal of work has been done by various observers, who tried to work out more rational methods. It must be confessed that the whole subject was somewhat chaotic, and the different modifications employed were all purely empirical. Now, however, we know the best dietetic means of combating diabetes, and for this knowledge we are indebted to Dr. F. M. Allen, who, by his painstaking and careful experimental work, has done much to put the dietetic treatment of the disease on a sound scientific basis.

Allen's Work on Diabetes.

Allen's experimental work has been so extensive that it is impossible here to devote more than a brief reference to its more important features. Allen removed the greater part of the pancreas from dogs, leaving behind a small fraction of the organ intact. He found that the ultimate fate of such dogs depended on the diet. When a dog with a very small amount of pancreas was fed on a high carbohydrate or fat diet, it gradually began to pass sugar in the urine, and soon developed all the symptoms of typical diabetes, with the result that death took place. Such a dog, when fed on a low diet, maintained good health and showed no signs whatever of diabetes. The dog, however, was not saved by limiting its carbohydrate intake and allowing large amounts of fat and protein; such diets invariably gave rise to diabetes, even when the carbohydrate diet was very low. It thus became obvious that in the case of partially de-pancreatised dogs, the correct treatment to maintain health was to give the lowest possible diet necessary for the needs of the animal. When this was exceeded, no matter what the nature of the food, diabetes tended to develop, with fatal results. Of course, in these animals the carbo-

hydrate must be restricted, but the important point is that this restriction alone is of little value unless the other food substances are also curtailed. These dogs, when kept thin, were found to be much less likely to develop diabetes than they were when allowed to get fat.

From these and other observations Allen argued that the correct treatment for human diabetes should consist in giving to the patient the minimum of food necessary for the requirements of the body, and it is on this principle that the modern treatment of diabetes is based.

It must not be forgotten in this connection that there is a very marked difference between the diabetes induced experimentally in animals and human diabetes. In experimental diabetes a definite lesion is the cause of the trouble. There is sufficient pancreas left to keep the dog in health, provided the small amount of tissue is not worn out, so to speak, by excessive food. If exhaustion of the essential pancreatic cells consequent on the giving of too much food is guarded against, there is no reason why the lesion should progress. The pancreatic fragment remaining is healthy, and there is no cause why it should not remain so. In human diabetes, however, the condition is otherwise. Here the disease is dependent on some change entirely different from the experimental removal of part of the pancreas, and from the very nature of things this change must be essentially progressive, otherwise the disease would never have manifested itself. That this progressive tendency can be accelerated by unsuitable diet is certain, but the point to remember is that in human diabetes we are dealing with two factors: (*a*) An essentially progressive lesion not present in experimental animals, and (*b*) the detrimental effect of improper diet. The latter factor we can eliminate, but we cannot always hope for the good results observed in dogs, because of the invariable presence of the first factor. If the tendency to progression of the disease is very marked, dietetic treatment will fail to a large extent, but if, as frequently seems to be the case, this factor is not a very active one,

then dietetic treatment will frequently give excellent results. All really depends on the nature of the lesion in human diabetes. In the cases in which dietetic treatment gives good results the symptoms before treatment were chiefly dependent on dietetic errors. In patients in whom dietetic treatment produces but slight and transitory improvement, the essential feature in the etiology is the inherent progressive nature of the pathological lesions present. Consideration of these points will help us to understand why modern dietetic treatment sometimes leads only to disappointment. Luckily there are some cases which show no very rapid inherent progress of the disease, and in such patients wonders may be accomplished by the use of modern dietetic methods. Many such patients, unless carefully treated, would, of course, get worse and die, but in these cases we do good by eliminating the one factor which we can control; the other factor, when present to a marked extent, necessitates the use of insulin.

The Principles of Modern Dietetic Treatment.

The modern treatment of severe diabetes consists essentially of two features. First, the patient is starved so as to get rid of glycosuria. He is then given diets consisting of progressively increasing amounts of the different foodstuffs in order to ascertain how much he can tolerate without glycosuria or marked ketosis. The minimum diet ultimately required for ordinary body needs is calculated from his weight and height, and no more than this is given. The amount of the different ingredients of the diet is arrived at by a system of testing as described below. It is essential that these changes in diet should be made gradually, in order that the tolerance should be raised, and to avoid such dangers as acidosis and digestive disturbances. It is bad treatment to render a patient sugar-free, and then immediately to put him on a comparatively large diet. The diet most suited to

the particular case must be worked out by giving the patient small amounts of food to begin with, and slowly working up to his limit. Frequently, in severe cases, it may be difficult or impossible to reach the theoretical minimum of calories necessary, but in many patients a gradual increase of tolerance sets in, and after many months a satisfactory diet may be assimilated. The diet must be limited by the glycosuria and ketosis; if at all possible, freedom from glycosuria must be maintained. Generally, a small amount of acetone is present, as indicated by Rothera's test; this cannot be avoided, but the ferric chloride test should, if possible, be negative. If the tolerance for sugar is so low that glycosuria is produced on a very low and quite insufficient diet, it may be necessary to reduce the weight of the patient considerably, when good results may be obtained.

Frequently, in mild cases, it is not necessary to make the patient undergo the rigorous treatment so essential in bad cases. Sometimes only a slight modification, such as a diminution in the total bulk with exclusion of fat, is all that is required to clear up the symptoms. In other patients the introduction of very low diets for a few days will result in a total disappearance of the glycosuria, and after this a suitable diet can easily be found. In severe cases, however, it is advisable that the patient should always undergo the full treatment. The various steps in connection with the treatment will now be described.

The Ketogenic-Antiketogenic Theory.

Within the last few years a great deal of work has been carried out, especially in America, dealing with the so-called ketogenic-antiketogenic theory of food combustion. The basis of this theory is nothing more than the well-worn physiological principle that in order to consume fat, sugar must be burned. That " fat is burned in the fire of carbohydrates " has been accepted as a physiological truth for very many years, but whether it is actually true or not

has not yet been finally proved. Accepting the theory as provisionally correct, an attempt has been made to ascertain more definitely the amount of sugar that has to be oxidised in order to consume a certain amount of fat. The result of a good deal of experimental work is exceedingly vague, but in general it would appear that the oxidation of 1 gram of sugar will result in the combustion of from 1 to 4 grams of fat. Indeed, the variation in the relationship of the amount of fat consumed by the combustion of a given weight of sugar is so great as to render the theory of but little practical value. Generally speaking, however, the fat of the diet should not exceed three times the amount of starch present. In this connection it must be remembered, as pointed out in Chapter I., that the only two substances which the body has ultimately to deal with are fat and sugar, for protein breaks down partly into sugar and partly into fat or fatty derivatives. It is also usually assumed that the glycerol of the fat furnishes its equivalent amount of sugar, though this is not quite certain. A diet of protein, fat and starch will ultimately furnish definite amounts of sugar and fat according to the following figures:

Diet.	*Sugar Formed from Diet.*	*Fat Formed from Diet.*
	Per Cent.	*Per Cent.*
Protein	58	46
Fat	10	90
Carbohydrate ..	100	—

Ordinary diets constructed in the usual way generally contain the necessary amount of carbohydrate to burn the fat. It has been the general custom for many years either to increase the carbohydrate or to decrease the fat when acidosis became severe, and the application of the ketogenic-antiketogenic theory does little more than this. Though interesting theoretically, we must remember that the idea put forward is only a theory, and so far, the conception has not proved of much practical use.

The Amount of Food Necessary in Diabetes.

It is now the custom to express food values in terms of calories. For clinical purposes it is sufficiently accurate to assume that—

1 gram carbohydrate = 4 calories.
1 ,, protein = 4 ,,
1 ,, fat = 9 ,,

The number of calories required in health varies from time to time, according to the activity of the subject and other conditions, but under ordinary circumstances it is found that an average individual requires a minimum of 25 to 30 calories per kilogram (2·2 pounds) of body weight per day in order to maintain health and weight. Thus a man of 60 kilograms would require from 1,500 to 1,800 calories, and in ordinary life would probably eat sufficient food to give a good deal more than this. If the weight of this man were reduced from 60 to 50 kilograms, then he could get along with 1,250 to 1,500 calories, and so would require less food. Normal healthy individuals generally eat more food than is necessary to produce 30 calories per kilogram, but this amount seems to be sufficient, at any rate, in diabetes.

Another important point to remember is that, whatever the nature of the diet, it is necessary to give some protein, and experience shows that the minimum amount of protein necessary is about 1 *gram per kilogram per day*. Often 1½ grams or more are actually taken by the healthy subject, but in diabetes it is seldom necessary to give more than 1·5 grams per kilogram as a maximum, and in general 1 gram suffices. In children it may be necessary to give 2 grams or more. Obviously, in building up a diabetic diet, it is important to ascertain the minimum calories and the minimum protein necessary. They are obtained from the weight of the patient, so that the first thing to do is to weigh the patient.

Diabetic subjects, especially elderly ones, are frequently very fat to begin with, and in calculating their permanent

diet it is best to allow sufficient calories for an average individual of similar age and height. This will result in keeping down their weight to the normal, a point of great importance in the treatment of many cases of the more severe type.

To ascertain the average normal weight of a subject of given age and height it is convenient to use tables such as the following: Table VII. gives the average weight (without clothes) for children of different ages and heights, while Tables VIII. and IX. give similar figures for adults. The height given in these tables includes 1 inch for boots in the case of adults over fifteen years of age, so that the true height is about 1 inch less than that given; in the case of children from one to fifteen years, the true height without boots is given. The height is expressed in feet and inches, and the weight in pounds.*

If the patient weighs 64 kilograms, but is 4 kilograms above the average for his age and height, we proceed to calculate his needs for a weight of 60 kilograms. As a minimum he would require a diet containing 60 grams of protein and 1,500 calories. Frequently, in the treatment of severe diabetes, it is a good plan to keep patients a few pounds below their ordinary weight, even if their weight does not exceed the average for their age and height.

Having estimated the requirements of the patient in this way, the next point is to ascertain the most suitable combination of foodstuffs for this particular patient. The diet of the diabetic must essentially be restricted in

* These figures are based on tables supplied by the Metropolitan Life Insurance Company, the Mutual Life Insurance Company, the Association of Life Insurance Directors and Actuarial Society of America, and other publications. The original tables are given in Joslin's "Diabetic Manual"; they show the weight for adults with clothes, and in the present tables 10 pounds have been subtracted in the case of males, and 6 pounds in the case of females, in order to arrive at the average true body weight.

TABLE VII.

Showing Average Weight of Children 1 to 15 Years Old for given Age and Height.

BOYS.

(*Height in feet and inches, taken without boots.*)

	2 6	2 10	3 1	3 3	3 5	3 7	3 9	3 11	4	4 2	4 4	4 6	4 8	4 10	5	5 2	5 4
Age.																	
1	22																
2		27															
3			32														
4				35	39												
5				35	39	42	46										
6					39	42	46	48									
7						42	46	49	54								
8							46	50	53	57							
9								50	53	58	62	68					
10									54	58	62	65					
11										61	61	68	77	78			
12											63	70	77	84	85		
13											66	71	78	85	91	99	
14											66	71	79	86	94	103	114
15													79	87	95	106	118

GIRLS.

(*Height in feet and inches, taken without boots.*)

	2 5	2 10	3 1	3 3	3 5	3 7	3 9	3 11	4	4 2	4 4	4 6	4 8	4 10	5	5 2	5 4
Age.																	
1	21																
2		27															
3			30														
4				33													
5				34	38	41											
6				34	38	41	45										
7					39	42	45	50									
8						42	45	50	51	56							
9								50	51	56	63						
10									54	57	63	69					
11										60	63	69	75				
12											63	69	75	83	91		
13											65	69	76	86	94	104	
14													78	88	96	104	112
15														89	100	106	118

1 kilogram = 2·2 pounds.

TABLE VIII.

Showing Average Weights of Adults 16 to 50 Years Old for given Age and Height.

MALES.

(*Height in feet and inches, taken in boots.*)

	5	5 2	5 4	5 6	5 8	5 10	6	6 2	6 4
Age.									
16	99	104	110	118	126	134	144	154	164
17	101	106	112	120	128	136	146	156	166
18	103	108	114	122	130	138	148	158	168
19	105	110	116	124	132	140	150	160	170
20	107	112	118	126	134	142	151	161	171
21	108	113	120	128	135	143	152	162	172
22	109	114	121	129	136	144	153	163	173
23	110	115	122	130	137	145	154	165	175
24	111	116	123	131	138	146	155	167	177
25	112	116	123	131	139	147	157	169	179
26	113	117	124	132	140	148	158	170	181
27	114	118	124	132	140	148	159	171	182
28	115	119	125	133	141	149	160	172	183
29	116	120	126	134	142	150	161	173	184
30	116	120	126	134	142	151	162	174	186
31	117	121	127	135	143	152	163	175	187
32	117	121	127	135	144	153	164	176	188
33	117	121	127	135	144	154	165	177	189
34	118	122	128	136	145	155	166	178	190
35	118	122	128	136	145	155	166	179	191
36	119	123	129	137	146	156	167	180	192
37	119	123	130	138	147	157	168	181	193
38	120	124	130	138	147	157	169	182	194
39	120	124	130	138	147	157	169	182	195
40	121	125	131	139	148	158	170	183	196
41	121	125	131	139	148	158	170	183	197
42	122	126	132	140	149	159	171	184	198
43	122	126	132	140	149	159	171	184	198
44	123	127	133	141	150	160	172	185	199
45	123	127	133	141	150	160	172	185	199
46	124	128	134	142	151	161	173	186	200
47	124	128	134	142	151	161	173	187	201
48	124	128	134	142	151	161	173	187	201
49	124	128	134	142	151	161	173	187	201
50	124	128	134	142	151	161	173	187	201
55	125	128	135	143	153	163	174	188	202

1 kilogram = 2·2 pounds.

TABLE IX.

Showing Average Weights of Adults 16 to 50 Years Old for given Age and Height.

FEMALES.

(*Height in feet and inches, taken in boots.*)

	4 8	4 10	5	5 2	5 4	5 6	5 8	5 10	6
Age.									
16	96	100	103	108	114	122	130	137	147
17	97	101	105	110	116	123	131	138	148
18	98	102	106	111	117	124	132	139	149
19	99	103	107	112	118	125	133	140	149
20	100	104	108	113	119	126	134	141	150
21	101	105	109	114	120	127	135	142	150
22	101	105	109	114	120	128	135	143	151
23	102	106	110	115	121	128	136	144	151
24	103	107	111	115	121	128	136	144	152
25	103	107	111	115	122	129	137	145	152
26	104	108	112	116	122	129	138	145	153
27	104	108	112	116	123	130	138	146	153
28	105	109	113	117	124	131	139	147	154
29	105	109	113	117	124	131	139	147	154
30	106	110	114	118	125	132	140	148	155
31	107	111	115	119	126	133	141	148	155
32	107	111	115	119	126	134	142	149	156
33	108	112	116	120	127	135	143	150	156
34	109	113	117	121	128	136	144	151	157
35	109	113	117	121	128	136	144	151	157
36	110	114	118	122	129	137	145	152	158
37	110	114	118	123	130	138	146	153	159
38	111	115	119	124	131	139	147	154	160
39	112	116	120	125	132	140	148	155	161
40	113	117	121	126	132	140	148	155	161
41	114	118	122	127	133	141	149	156	162
42	114	118	123	127	133	141	149	156	163
43	115	119	123	128	134	142	150	157	164
44	116	120	124	129	135	143	151	158	165
45	116	120	124	129	135	143	151	158	165
46	117	121	125	130	136	144	152	159	166
47	117	121	125	130	136	145	153	160	167
48	118	122	126	131	137	146	154	161	168
49	118	122	126	131	137	146	155	162	169
50	119	123	127	132	138	146	155	163	170
55	119	123	127	132	138	147	157	164	171

1 kilogram = 2·2 pounds.

carbohydrate, and it is rare in cases of any severity to find a patient who can take more than 80 or 100 grams without producing glycosuria. Some patients, especially at the beginning of treatment, can take only 5 grams of carbohydrate or even less, but generally their tolerance increases as the result of treatment, though sometimes they are permanently restricted to very minimal amounts. In such cases a protein diet with some fat must be relied upon. A certain amount of carbohydrate in the diet is of great value in preventing acidosis, but occasionally one sees a case in which the necessary calories have to be made up almost entirely from protein and fat with a few ounces of cooked vegetables, and yet no signs of acidosis may be in evidence. It is advisable, in all cases, to give as a permanent diet the maximum amount of carbohydrate that the patient can tolerate without producing glycosuria. After the patient is rendered sugar-free by starvation, increasing amounts of food are given day by day until the patient passes sugar. This gives his tolerance limit, and on this knowledge his final diet must be worked out.

Details of Dietetic Treatment.

The exact method employed must vary according to circumstances, but in a case of any severity it is best to begin at once to get rid of glycosuria by means of starvation. It is very seldom that any danger is associated with this plan. In a few extremely rare instances, fasting has given rise to dangerous coma, but the condition can be relieved by giving food. If the patient is very fat and the symptoms grave, it may be advisable to use a fat-free diet for a few days previous to the fasting treatment. Personally, I make all my patients fast directly, without any preliminary change in diet, and have, so far, never had any ill effects. Patients suffering from marked tubercular and other grave pathological lesions should not be fasted.

Fasting Treatment.

Fasting as carried out is not really starvation, since the patient is allowed to take as much as is desired of tea, black coffee, and beef tea. Before treatment the bowels should be thoroughly opened, but beyond this no special attention is required. For the first day or two it is perhaps best to keep the patient in bed, but this is not strictly necessary, though it tends to conserve energy. Many patients are more comfortable when up and about. Smoking may be allowed. If marked weakness is present, a little alcohol (2 to 4 ounces a day) may be given, but if possible it is best to avoid this. Patients in a condition of apparently grave weakness will frequently stand fasting extraordinarily well, and unless the condition is extremely grave, fasting ought to be tried. If this is definitely contra-indicated, such patients should be deprived of carbohydrate and fat, and fed with protein until the condition improves, when more drastic means may frequently be adopted with safety and success. Naturally, each medical man will have to decide for himself whether or not the patient is in a condition to be fasted.

The average patient experiences very little discomfort from fasting, and after the first day does not usually complain. The time required to get rid of glycosuria varies, but is generally from three to five days; sometimes it takes ten days or more, but in such cases it is best to give some protein after five or six days and then to fast again. In very rare instances glycosuria persists in spite of starvation, but this is unusual except in the most severe type. The general ease with which glycosuria yields to fasting is really very remarkable, and this part of the treatment does not as a rule give much trouble. The real battle begins later, when we try to build up a suitable permanent diet. The urine from fasting patients must be collected, and a sample of the daily output constantly examined for sugar and ketone bodies. In the milder cases acetone may be more abundant during

fasting than it was to begin with, but in the severer cases it decreases markedly with fasting. Frequently, in early cases there is no acetonuria to begin with, and in such patients acetone nearly always appears on fasting. This does no harm, and need not cause alarm. It is more or less a physiological process, which is seen in its true light when we remember that every normal healthy individual will produce acetone in the urine when starved. In cases with a tendency to acidosis, fasting is generally the best treatment, and, on the whole, there is little danger of coma during the process. When definite indications of coma intervene the fast must be stopped, and carbohydrate and protein given freely. When the critical period passes over the fasting may be resumed. When the urine becomes free from sugar the blood-sugar should be estimated, for it is by no means uncommon, especially in elderly patients, to find a sugar-free urine with a blood-sugar as high as 0·25 to 0·3 per cent., or even more. Here the renal threshold for sugar is raised, a condition frequently associated with definite changes in the kidneys, and examination of the urine gives little or no clue to the results of treatment. When a high blood-sugar value persists, fasting must be persevered with. In such cases blood-sugar estimations alone can be used as a guide. The ideal is to obtain a blood-sugar concentration as near as possible to the normal 0·1 per cent., and this is frequently accomplished. After all, everything depends on the blood-sugar concentration, and in the light of what has already been said in Chapter II. it is obvious that a much better idea of the condition of affairs is always to be obtained from the estimation of blood-sugar rather than from examination of the urine. The urine is merely an index, but even in patients with normal sugar thresholds we cannot tell from the urine whether the blood-sugar is 0·1 per cent. or as high as 0·18 per cent. Naturally, when the blood-sugar is high, glycosuria will be much more easily induced when food is given than when the blood-sugar content is low.

Having obtained freedom from glycosuria, associated

if possible with a low blood-sugar content, the patient continues to fast for 24 hours more. The next step in the process is to give graduated diets consisting of protein, fat, and carbohydrate. Protein and carbohydrate in small amounts are given chiefly for the first few days, and the fat is gradually added. It is very rarely the case that a diabetic patient can take a large bulk of food without getting glycosuria and ketosis, so that it is generally necessary in all severe cases to give substances

TABLE X.

Showing Carbohydrate Content of Various Vegetables and Fruits.

Group.	One Ounce contains—	
A	1 gram carbohydrate ..	Cabbage, cauliflower, Brussels sprouts, lettuce, spinach, cucumbers, asparagus, marrow, rhubarb, celery, mushrooms, tomatoes, watercress, sea kale, radishes, leeks, grape fruit, endive.
B	2 grams carbohydrate ..	Carrots, onions, turnips, beets, French beans.
C	3 grams carbohydrate ..	Oranges, strawberries, gooseberries, cranberries, peaches, pineapple, water melon.
D	4 grams carbohydrate ..	Green peas, artichokes, parsnips, apples, pears, currants, cherries, raspberries, apricots.
E	6 grams carbohydrate ..	Potatoes, plums, prunes, bananas.

containing very little food material but is bulky enough to ease the pangs of hunger. For this purpose vegetables are largely used. These substances are rich in cellulose material, and vary to some extent in their carbohydrate content, but as a rule they may be regarded as containing approximately the amounts of carbohydrate indicated in Table X., in which they are divided into five groups. One ounce of group A contains 1 gram carbohydrate; 1 ounce of group B, 2 grams, etc. There is a

certain amount of nitrogen present in these vegetables, but to what extent it represents assimilable protein is unknown, and, indeed, the same remark is true of the carbohydrate also. Only very small traces of fat are present, so that for practical purposes they may be regarded as containing carbohydrate only, and the amount given in the table is probably above the true carbohydrate content, especially when they are cooked. In patients with little or no sugar tolerance, bulk of diet can be obtained by using vegetables of group A which have been boiled in three or four changes of water. For such patients the best vegetables to use are cabbage, celery, and spinach. Vegetables cooked in this way contain only traces of carbohydrate; they are not very appetising, but they are much improved by the addition of a little salt and some beef tea. In these very severe cases the patient is practically incapable of using any carbohydrate. He must live, at least for a time, on fat and protein. Table X. can be used to build up the vegetable content of his diet, and the relative value of the different groups can be easily calculated. Thus, 6 ounces of cabbage may be substituted by $1\frac{1}{2}$ ounces of green peas or by 2 ounces of orange. As a general rule, it is advisable to restrict the very severe type of case to vegetables of groups A and B, owing to the danger of causing glycosuria by taking slight excess of the other groups richer in carbohydrate; also, the higher the average carbohydrate content the more liability there is for variations in the content.

It frequently happens that patients require a substitute for bread, even if this substitute should contain no nutriment whatever, and for this purpose bran biscuits are excellent. Though they contain no nourishment, they are very useful in that they give the patient something which looks and tastes not very unlike bread. These biscuits are most valuable in all sorts of diets where the bread ration must be kept very low; a certain amount of butter and eggs may be mixed with the bran when these substances are allowed in the diet.

Bran Biscuits.

Allen gives the following directions for the making of bran biscuits. They consist of

Bran, weighed dry	=	2 ounces.
Agar-agar powdered	=	¾ ounce.
Cold water	=	3½ ounces.

The bran is tied in cheese cloth and hung under the cold water tap to wash; it is kneaded or stirred from time to time until the water runs through clear. This takes about ½ hour or more, and it is most important that this should be done thoroughly. The agar is mixed in 3½ ounces cold water and brought to the boil; the hot agar solution is then added to the washed bran. The mixture is moulded into three cakes, placed in a pan, and when firm and cold baked until dry and crisp. Salt may be used according to taste. It is most important to choose a suitable bran, since many so-called brans are rich in carbohydrates. The variety employed for feeding cattle should be used, as it contains the minimum amount of starchy material, and is very satisfactory when washed under the tap as directed.

In making up suitable diets Table XI. may be used; it contains a list of practically all the articles required in the treatment of diabetes. This table should be employed in conjunction with Table X. Any diet made up from these tables, and containing approximately the same amount of protein, fat, and carbohydrates as is indicated in the specimen diets, will be suitable. Owing to the great variations in the composition of the same articles of food, it is impossible to furnish tables that are at all accurate; only a general indication of the composition of the various substances can, of course, be given, and different authorities quote different figures. However, the average figures given here will be found quite satisfactory in practice.

The patient should have a fasting day each week

while the diet is being built up, whether any sugar appears in the urine or not. If he succeeds in taking all the diets suggested without passing sugar or showing much ketosis, he may remain on the last diet for a few days, when attempts should be made to lower the fat and raise the carbohydrate, and perhaps the protein as well. If glycosuria appears while one of the earlier diets is being

TABLE XI.

SHOWING THE APPROXIMATE CONTENT IN GRAMS OF PROTEIN, FAT, AND CARBOHYDRATE IN 1 OUNCE OF FOODS.

	Carbohydrate.	*Protein.*	*Fat.*	*Calories.*
Almonds	4	5	14	**168**
Bread (brown) ..	13	1·2	0	**65**
Bread (white)	15	2	0	**75**
Brazil nuts	2	5	19	**204**
Butter	0	0	23	**212**
Broth	0	1	0	**5**
Bacon	0	3	18	**180**
Cream (thin) ..	1	1	6	**65**
Cream (thick) ..	1	1	20	**190**
Chicken	0	6	1	**34**
Cheese	0	8	10	**130**
One egg	0	6	6	**80**
Fish (cod, whiting, haddock) ..	0	5	0	**20**
Meat (lean) ..	0	6	3	**51**
Milk	1·5	1	1	**19**
Margarine	0	0	23	**212**
Oatmeal (dry weight)	18	4	2	**112**
Potato	6	0·5	0	**30**
Shredded wheat ..	21	3	0	**103**
Three oysters ..	2	3	0	**25**

taken, the patient should be fasted till the sugar disappears, and this diet should be persisted with for some days afterwards. If no sugar then appears, the higher diets are given, but in such cases it is often advisable to proceed slowly, and it is a good plan to give each diet for two or three days before proceeding to the next highest. If glycosuria persists while on this early diet, the carbo-

hydrate content must be reduced to about half or so, and for some time the patient must be restricted to this amount; at the same time the protein and fat are gradually increased. If ketonuria becomes very marked, the patient should be starved for a day or two and the fat ration reduced. Whenever glycosuria appears, no matter at what stage, the patient should be fasted until it disappears. All sorts of plans may be necessary, and no hard-and-fast rules can be given; some cases present great difficulties, but our goal is to increase the patient's tolerance, so that ultimately he may be able to take a diet on which he can live without showing glycosuria and ketonuria. Our success in this will depend on our persistence and the progress of the disease. In very severe cases we can only hope that the very low diet necessary will ultimately result in increased tolerance; if it does not, the case is hopeless as far as dieting is concerned, and insulin must be used. Finally, it is important to explain carefully to the patient what the position really is, and how essential it is that directions should be implicitly obeyed, as far as it is in his power to do so. Intelligent patients should be taught to test their own urine, and should learn how to get rid of glycosuria when it occurs. Not infrequently our best efforts are rendered useless by stupidity or lack of stamina on the part of patients, but, in spite of this, the occasional triumphs encountered make a determined effort worth while even in apparently severe cases.

It may take many months to build up a suitable diet, or this may prove impossible, and the patient may go steadily down-hill in spite of all our endeavours. The more experience we have of diabetes the more hopefully do we treat even apparently desperate cases, for now and again we have our reward. If diet proves unsuccessful in spite of all our endeavours, we must fall back on insulin.

The following specimen diets are similar to those used at St. Thomas's Hospital. The amounts given here are calculated for a patient weighing 65 kilograms.

FIRST DAY.

	Carbo-hydrate.	*Protein.*	*Fat.*	*Calories.*
Breakfast :				
Tea with one teaspoonful thin cream	—	—	0·5	—
2 ounces cabbage (boiled three times)	1	—	—	—
Lunch :				
Beef tea	—	—	—	—
2 ounces cabbage (boiled three times)	1	—	—	—
Tea :				
Tea or coffee with one teaspoonful thin cream	—	—	0·5	—
2 ounces raw lettuce ..	2	—	—	—
Dinner :				
Tea or coffee with one teaspoonful thin cream	—	—	0·5	—
4 ounces cabbage (boiled three times)	2	—	—	—
One bran biscuit ..	—	—	—	—
Half hard-boiled egg ..	—	4	3	—
Total ..	6	4	4	76

SECOND DAY.

	Carbo-hydrate.	*Protein.*	*Fat.*	*Calories.*
Breakfast :				
Tea or coffee with ¼ ounce thin cream	—	—	1·5	—
4 ounces cabbage (boiled three times)	2	—	—	—
One bran biscuit ..	—	—	—	—
Lunch :				
Beef tea	—	—	—	—
4 ounces raw lettuce ..	4	—	—	—
One egg (2 ounces) ..	—	8	6	—
Tea :				
Tea with one teaspoonful thin cream	—	—	0·5	—
2 ounces raw lettuce ..	2	0·5	—	—
Half hard-boiled egg ..	—	4	3	—
One bran biscuit ..	—	—	—	—
Dinner :				
Tea or coffee with one teaspoonful thin cream	—	—	0·5	—
4 ounces cabbage (boiled three times)	2	—	—	—
Half bran biscuit ..	—	—	—	—
Total ..	10	12	11	187

THIRD DAY.

	Carbo-hydrate.	*Protein.*	*Fat.*	*Calories.*
Breakfast :				
Tea or coffee with ¼ ounce thin cream	—	—	1·5	—
6 ounces raw lettuce ..	6	1·5	—	—
One egg (2 ounces) ..	—	8	6	—
One bran biscuit ..	—	—	—	—
Lunch :				
Beef tea	—	—	—	—
4 ounces cabbage ..	4	1	—	—
1 ounce white fish ..	—	5	—	—
Tea :				
Tea with ¼ ounce thin cream	—	—	1·5	—
One egg (2 ounces) ..	—	8	6	—
3 ounces raw lettuce ..	3	0·75	—	—
Dinner :				
2 ounces lettuce ..	2	—	—	—
3 ounces cabbage ..	3	—	—	—
One egg (2 ounces) ..	—	8	6	—
Tea with ¼ ounce thin cream	—	—	1·5	—
Total ..	18	32	22	398

FOURTH DAY.

	Carbo-hydrate.	*Protein.*	*Fat.*	*Calories.*
Breakfast:				
Tea or coffee with ¼ ounce thin cream	—	—	1·5	—
6 ounces raw lettuce ..	6	1·5	—	—
¾ ounce brown bread ..	10	1	—	—
One egg (2 ounces) ..	—	8	6	—
Lunch:				
Beef tea	—	—	—	—
4 ounces cabbage ..	4	1	—	—
1 ounce white fish ..	—	5	—	—
One egg (2 ounces) ..	—	8	6	—
Tea:				
Tea with ¼ ounce thin cream	—	—	1·5	—
3 ounces cabbage ..	2	0·75	—	—
2 ounces lettuce ..	2	0·5	—	—
One egg (2 ounces) ..	—	8	6	—
One bran biscuit ..	—	—	—	—
Dinner:				
Beef tea	—	—	—	—
3 ounces white fish ..	—	15	—	—
½ ounce potatoes ..	3	0·5	—	—
4 ounces lettuce ..	4	1	—	—
Total ..	31	50	21	513

FIFTH DAY.

	Carbo-hydrate.	*Protein.*	*Fat.*	*Calories.*
Breakfast :				
Tea or coffee with ¼ ounce thin cream	—	—	1·5	—
6 ounces raw lettuce ..	6	0·5	—	—
¾ ounce brown bread ..	10	1	—	—
One egg (2 ounces) ..	—	8	6	—
Lunch :				
Beef tea	—	—	—	—
4 ounces cabbage ..	4	1	—	—
3 ounces white fish ..	—	15	—	—
One egg (2 ounces) ..	—	8	6	—
Tea :				
Tea with ¼ ounce thin cream	—	—	1·5	—
3 ounces cabbage ..	3	—	—	—
2 ounces lettuce ..	2	—	—	—
One egg (2 ounces) ..	—	8	6	—
¾ ounce brown bread ..	10	1	—	—
Dinner :				
Beef tea	—	—	—	—
3 ounces white fish ..	—	15	—	—
½ ounce potatoes ..	3	0·5	—	—
4 ounces lettuce ..	4	1	—	—
One bran biscuit ..	—	—	—	—
Total ..	42	59	21	593

SIXTH DAY.

	Carbo-hydrate.	*Protein.*	*Fat.*	*Calories.*
Breakfast :				
Coffee with ½ ounce thin cream	—	—	3	—
6 ounces lettuce or salad from Group A	6	1·5	—	—
One egg (2 ounces) ..	—	8	6	—
¼ ounce butter	—	—	6	—
One bran biscuit ..	—	—	—	—
Lunch :				
Beef tea	—	—	—	—
5 ounces white fish (cod or haddock)	—	25	—	—
6 ounces cabbage or vegetable of Group A	6	1·5	—	—
2 ounces orange or fruit from Group C	8	—	—	—
Tea :				
Tea with ½ ounce thin cream	—	—	3	—
4 ounces celery or salad from Group A ..	4	1	—	—
¼ ounce butter ..	—	—	6	—
One bran biscuit ..	—	—	—	—
Dinner :				
Beef tea	—	—	—	—
5 ounces white fish (sole or flounder)	—	20	—	—
5 ounces spinach ..	5	2·5	—	—
4 ounces apple or pear	16	—	—	—
Total ..	45	59	24	632

SEVENTH DAY.

	Carbo-hydrate.	*Protein.*	*Fat.*	*Calories.*
Breakfast :				
Black coffee with ½ ounce thin cream	—	—	3	—
One bran biscuit ..	—	—	—	—
¼ ounce butter	—	—	6	—
6 ounces tomatoes or vegetable from Group A	6	1·5	—	—
One egg (2 ounces) ..	—	8	6	—
Lunch :				
Beef tea	—	—	—	—
4 ounces white fish (haddock or cod)	—	20	—	—
6 ounces cabbage ..	6	1·5	—	—
1 ounce cheese (Cheddar)	—	7	9	—
One bran biscuit ..	—	—	—	—
4 ounces orange or fruit from Group C	12	1	—	—
Tea :				
Tea with ½ ounce thin cream	—	—	3	—
One bran biscuit ..	—	—	—	—
5 ounces lettuce or salad from Group A	5	1·3	—	—
¼ ounce butter	—	—	6	—
Dinner :				
Beef tea	—	—	—	—
5 ounces flounder or sole	—	20	—	—
3 ounces carrots or vegetable from Group B	6	1	—	—
4 ounces apple or fruit from Group D	16	—	—	—
Total ..	51	61	33	745

EIGHTH DAY.

Fasting day. Patient to have beef tea, coffee, and tea.

NINTH DAY.

	Carbo-hydrate.	*Protein.*	*Fat.*	*Calories.*
Breakfast :				
Black coffee with ½ ounce thin cream	—	—	3	—
One egg (2 ounces) ..	—	8	6	—
6 ounces tomatoes or salad from Group A	6	1·5	—	—
½ ounce salad oil ..	—	—	14	—
One bran biscuit ..	—	—	—	—
¼ ounce butter	—	—	6	—
Lunch :				
Beef tea	—	—	—	—
4 ounces white fish (flounder or sole)	—	20	—	—
4 ounces French beans or vegetable from Group B	8	1·5	—	—
½ ounce cheese (Cheddar)	0·5	3·5	4·5	—
¼ ounce butter	—	—	6	—
4 ounces orange or fruit from Group C	12	1·2	—	—
One bran biscuit ..	—	—	—	—
Tea :				
Tea with ½ ounce thin cream	—	—	3	—
One bran biscuit ..	—	—	—	—
¼ ounce butter	—	—	6	—
4 ounces lettuce or salad from Group A	4	1	—	—
Dinner :				
Beef tea	—	—	—	—
5 ounces white fish (cod or haddock)	—	25	—	—
5 ounces cucumber or vegetable from Group A	5	—	—	—
5 ounces apple or fruit from Group D	20	—	—	—
Total ..	55	62	48	900

TENTH DAY.

	Carbo-hydrate.	*Protein.*	*Fat.*	*Calories.*
Breakfast :				
Coffee with ½ ounce milk	0·75	0·5	0·5	—
4 ounces white fish (flounder or sole)	—	16	—	—
4 ounces milk	5	4	4	—
¼ ounce butter	—	—	6	—
4 ounces tomatoes or salad from Group A	4	1	—	—
½ ounce salad oil ..	—	—	14	—
One bran biscuit ..	—	—	—	—
Lunch :				
Beef tea	—	—	—	—
3½ ounces chicken ..	—	21	4·5	—
6 ounces cabbage ..	6	1·5	—	—
¼ ounce butter	—	—	6	—
4 ounces celery or salad from Group A	4	1	—	—
One bran biscuit ..	—	—	—	—
Tea :				
Tea with ½ ounce thin cream	—	—	3	—
One bran biscuit ..	—	—	—	—
½ ounce butter	—	—	11·5	—
4 ounces strawberries or fruit from Group C	12	1	—	—
Dinner :				
Beef tea	—	—	—	—
Two eggs	—	16	12	—
6 ounces French beans or vegetable from Group B	12	1	—	—
½ ounce shredded wheat	11·5	1·5	—	—
½ ounce thin cream ..	—	—	3	—
Total ..	55	64	64	1,052

ELEVENTH DAY.

	Carbo-hydrate.	*Protein.*	*Fat.*	*Calories.*
Breakfast :				
Coffee with ½ ounce milk	0·75	0·5	0·5	—
1 ounce bacon	—	3	18	—
One egg (2 ounces) ..	—	8	6	—
½ ounce butter	—	—	11·5	—
6 ounces spinach or vegetable from Group A	6	1	—	—
One bran biscuit ..	—	—	—	—
Lunch :				
Beef tea	—	—	—	—
5 ounces white fish (cod or haddock)	—	25	—	—
6 ounces cabbage or vegetable from Group A	6	1·5	—	—
1 ounce brown bread ..	13	1·25	0·25	—
½ ounce butter	—	—	11·5	—
4 ounces grape fruit or salad from Group A	4	1	—	—
Tea :				
Tea with ½ ounce milk	0·75	0·5	0·5	
1 ounce brown bread ..	13	1·25	0·25	—
½ ounce butter	—	—	11·5	—
One egg (2 ounces) ..	—	8	6	—
Dinner :				
Beef tea	—	—	—	—
4 ounces white fish (flounder or sole)	—	16	—	—
4 ounces cauliflower or vegetable from Group A	4	1	—	—
¾ ounce butter	—	—	17·5	—
3 ounces orange or fruit from Group C	9	—	—	—
Total ..	56	68	83	1,243

TWELFTH DAY.

	Carbo-hydrate.	*Protein.*	*Fat.*	*Calories.*
Breakfast :				
Coffee with ½ ounce milk	0·75	0·5	0·5	—
1½ ounces bacon ..	—	4·5	27	—
One egg (2 ounces) ..	—	8	6	—
½ ounce butter.. ..	—	—	11·5	—
1 ounce brown bread ..	13	1·25	0·25	—
4 ounces lettuce or salad from Group A	4	1·0	—	—
Lunch :				
Beef tea	—	—	—	—
3 ounces veal cutlet or chicken or meat	—	18	6	—
3 ounces potatoes ..	15	3	—	—
5 ounces watercress or salad from Group A	5	1·25	—	—
½ ounce salad oil ..	—	—	14	—
Tea :				
Tea with ½ ounce milk	0·75	0·5	0·5	—
1 ounce brown bread ..	13	1·25	0·25	—
½ ounce butter ..	—	—	11·5	—
One egg (2 ounces) ..	—	8	6	—
Dinner :				
Beef tea	—	—	—	—
3½ ounces white fish (cod or haddock)	—	17·5	—	—
One bran biscuit ..	—	—	—	—
1 ounce butter ..	—	—	23	—
5 ounces celery or vegetable from Group A	5	1·25	—	—
½ ounce salad oil ..	—	—	14	—
Total ..	56	66	120	1,568

THIRTEENTH DAY.

	Carbo-hydrate.	*Protein.*	*Fat.*	*Calories.*
Breakfast :				
Coffee with ½ ounce milk	0·75	0·5	0·5	—
2 ounces bacon ..	—	6	36	—
One egg (2 ounces) ..	—	8	6	—
½ ounce butter ..	—	—	11·5	—
1 ounce brown bread ..	13	1·25	0·25	—
4 ounces lettuce or salad from Group A	4	1	—	—
½ ounce salad oil ..	—	—	14	—
Lunch :				
Beef tea	—	—	—	—
2 ounces chicken ..	—	12	2	—
2 ounces ham	—	8	16	—
1 ounce white bread ..	15	2	0·5	—
½ ounce butter.. ..	—	—	11·5	—
5 ounces tomatoes or salad from Group A	5	1·25	—	—
½ ounce salad oil ..	—	—	14	—
Tea :				
Tea with ½ ounce milk	0·75	0·5	0·5	—
1 ounce brown bread..	13	1·25	0·25	—
½ ounce butter.. ..	—	—	11·5	—
4 ounces grape fruit or fruit from Group A	4	1	—	—
Dinner :				
Beef tea	—	—	—	—
4 ounces cod or haddock	—	20	—	—
½ ounce cheese.. ..	0·5	3·5	4·5	—
½ ounce butter.. ..	—	—	11·5	—
One bran biscuit ..	—	—	—	—
4 ounces cabbage or vegetable from Group A	4	1	—	—
Total ..	60	67	140	1,768

FOURTEENTH DAY.

Fasting day. Diet same as on No. 8 day.

FIFTEENTH DAY.

	Carbo-hydrate.	*Protein.*	*Fat.*	*Calories.*
Breakfast :				
Coffee with ½ ounce milk	0·75	0·5	0·5	—
2 ounces bacon ..	—	6	36	—
1 ounce brown bread ..	13	1·25	0·25	—
One egg (2 ounces) ..	—	8	6	—
½ ounce butter.. ..	—	—	11·5	—
4 ounces grape fruit or fruit from Group A	4	1	—	—
Lunch :				
Beef tea	—	—	—	—
2 ounces chicken ..	—	12	2	—
2 ounces ham	—	8	16	—
1 ounce white bread ..	15	2	0·5	—
½ ounce butter.. ..	—	—	11·5	—
4 ounces cabbage or vegetable from Group A	4	1	—	—
Tea :				
Tea with ½ ounce milk	0·75	0·5	0·5	—
1 ounce brown bread ..	13	1·25	0·25	—
¾ ounce butter ..	—	—	17·5	—
4 ounces tomatoes or salad from Group A	4	1	—	—
½ ounce salad oil ..	—	—	14	—
Dinner :				
Beef tea	—	—	—	—
3 ounces shoulder of mutton	—	15	27	—
3 ounces cabbage ..	3	0·75	—	—
½ ounce butter.. ..	—	—	11·5	—
1 ounce cheese.. ..	1	7	9	—
One bran biscuit ..	—	—	—	—
Total ..	58	65	164	1,968

SIXTEENTH DAY.

	Carbo-hydrate.	*Protein.*	*Fat.*	*Calories.*
Breakfast :				
Coffee with ½ ounce milk	0·75	0·5	0·5	—
2 ounces bacon ..	—	6	36	—
One egg (2 ounces) ..	—	8	6	—
½ ounce butter.. ..	—	—	11·5	—
1 ounce brown bread ..	13	1·25	0·25	—
4 ounces grape fruit or fruit from Group A	4	1	—	—
Lunch :				
Beef tea	—	—	—	—
2 ounces chicken ..	—	12	2	—
2 ounces ham	—	8	16	—
1 ounce white bread ..	15	2	0·5	—
½ ounce butter.. ..	—	—	11·5	—
4 ounces endive or salad from Group A	4	1	—	—
½ ounce salad oil ..	—	—	14	—
Tea :				
Tea with ½ ounce milk	0·75	0·5	0·5	—
1 ounce brown bread ..	13	1·25	0·25	—
1 ounce butter.. ..	—	—	23	—
5 ounces tomatoes or salad from Group A	5	1·25	—	—
½ ounce salad oil ..	—	—	14	—
Dinner :				
Beef tea	—	—	—	—
4 ounces rump steak ..	—	16	24	—
1 ounce cheese (Cheddar)	1	7	9	—
1 ounce butter.. ..	—	—	23	—
3 ounces cabbage or vegetable from Group A	3	0·75	—	—
One bran biscuit ..	—	—	—	—
Total ..	59	66	192	2,228

SOME RECIPES SUITABLE FOR PATIENTS ON DIABETIC DIET.

Since the food of the diabetic patient is necessarily somewhat restricted both in amount and in variety of material, it is important that the diet should be served as attractively as possible. The Sisters of my wards have kindly supplied me with the following recipes which they have found very useful in preparing diets for diabetic patients at St. Thomas's Hospital. The materials used are limited to those included in the scheme of diets just given. Similar recipes may be used for diabetic patients on insulin treatment (see diets, p. 171). If the patient prefers it, 1 ounce of bread may be substituted by 2 ounces of potatoes.

Stuffed Tomatoes.

Take 2 ounces of finely chopped meat or ham and season with pepper and salt. Cut off the top of a tomato, scoop out the inside, and mix with the chopped meat. Stuff the shell of the tomato with the mixture and replace the top. Place round it 2 ounces of cabbage or any other " Group A " vegetable, and serve very hot.

Different Methods of Serving Potatoes.

(*a*) **Potato Balls.**—Mix 2 ounces of mashed potatoes with ½ ounce butter and ½ ounce cream. Season with pepper and salt, roll into balls, and bake till brown, or fry if preferred.

A savoury can be made from the above materials by the addition of ½ ounce cheese.

(*b*) **Potato Pie.**—Mix 2 ounces potatoes with 4 ounces of " Group A " vegetables. Add ½ ounce butter and bake in a casserole.

Savoury Custard.

Beat up two eggs with 5 ounces of beef tea, season with salt and pepper, and bake in a slow oven till set and slightly browned.

Cauliflower au Gratin.

Wash the cauliflower, boil it till tender, and then put it in a baking dish. Season with salt and pepper, pour over it ½ ounce cream, and sprinkle ½ ounce grated cheese on the top. Bake till slightly browned and serve very hot.

Sardines on Toast.

Toast ½ ounce of bread and spread on it ½ ounce butter. Lay the sardines on the toast, sprinkle with salt and pepper, and serve very hot. Garnish with parsley.

Fish Cream.

Pound some white fish, season it, and mix well with ½ ounce cream. Sprinkle over it ½ ounce cheese and bake till slightly browned.

Iced Grape Fruit.

Remove the soft part of the fruit from the rind and weigh out the required quantity. Then replace it in the rind, flavour with a small quantity of maraschino, and surround the fruit with ice before serving.

Scotch Eggs.

Hard boil one egg. Make a forcemeat of finely chopped ham, ½ ounce cream, and 2 ounces potatoes. Cover the egg with it and fry in ½ ounce butter. Cut the egg in half to show the yolk, and serve surrounded with 4 ounces "Group A" vegetables.

Œufs durs au Fromage.

Cut one or two hard-boiled eggs in slices and lay them in a baking dish. Pour over them ½ ounce cream and sprinkle ½ ounce grated cheese on the top. Serve very hot.

Poached Eggs on Spinach.

Cook the spinach and pass it through a hair sieve. Make it into a flat mould and lay the poached eggs on the top.

Baked Eggs.

Break an egg into a casserole, season with pepper and salt, add ¼ ounce butter, and bake till the egg is set.

Fish Pie.

Put some white fish in a baking dish, season, and pour over it ½ ounce cream. Mash 2 ounces potatoes, heat in a saucepan with ½ ounce butter, and cover the fish with it. Bake till slightly brown.

Bacon Rolls.

Chop finely one hard-boiled egg and 3 ounces white fish. Make it into a paste with ½ ounce cream, and mould into balls. Roll each ball in a rasher of bacon (½ ounce) and fry in ½ ounce butter.

Fish Salad.

Make a salad of lettuces, tomatoes, watercress, radishes, etc., and add some cooked white fish. Pour over it a mayonnaise sauce.

Buttered Eggs and Tomatoes.

Toast ½ ounce bread. Beat up an egg and heat in a saucepan with ½ ounce butter. Bake the tomatoes and serve round the egg, or mix both together.

Fish or Meat Rissoles.

4 ounces meat and ½ ounce beef dripping, or 4 ounces fish and ½ ounce butter. Mince the meat or fish finely and mix well with ½ ounce butter and 1 ounce mashed potatoes. Roll into balls, cover with yolk of egg and ½ ounce bread-crumbs. Fry in ½ ounce butter and serve with "Group A" vegetables.

Stuffed Marrow.

Cook the marrow till tender. Cut in half, scoop out the seeds and fill the hollow with finely chopped ham or meat. Put the two halves together and stew gently in beef tea, or bake in the oven with ½ ounce of grated cheese sprinkled on the top.

CHAPTER IX

THE TREATMENT OF DIABETES BY MEANS OF INSULIN

For many years past it has been well known that the pancreas elaborated some substance which was essential for the metabolism of carbohydrate, but, until quite recently, all attempts to separate this substance proved unsuccessful. On many occasions pancreatic extracts of different kinds were tried by various investigators both in diabetic and in normal animals, but in the majority of cases no success was obtained, though occasionally an extract was prepared which seemed to produce some effect at least in reducing the blood-sugar content. Some few years ago, for instance, Scott isolated a substance which definitely lowered the blood-sugar in animals, but its action was weak and inconstant. Until two years ago, the general impression prevalent among research workers was that the hypothetical pancreatic substance which governed carbohydrate metabolism in the body was of so labile a nature that attempts at its isolation rendered it inactive. After many failures by previous investigators, the problem was taken up by Banting in Toronto, and successfully solved. To Banting belongs the credit of having first isolated from the pancreas a preparation which was capable of reducing the blood-sugar in animals and man. This internal pancreatic secretion was first separated in a crude chemical form, and in this condition, when injected into animals in sufficient amount, was found to be capable of reducing the blood-sugar to such an extent that life was no longer possible. Banting's fundamental discovery that a pancreatic product could be obtained which influenced the utilisation of carbohydrate in the body paved the way for further work, with the result that it is now possible to procure a very much purer

substance. To this compound the name *insulin* has been given, but it must not be imagined that insulin is by any means a chemically pure entity. It probably consists of a mixture of various bodies containing only a comparatively small amount of the active principle. Of the exact chemical nature of insulin we at present know nothing. In the pancreas its presence appears to be limited to the islets of Langerhans.

The isolation of insulin has completely changed the outlook as far as the treatment of diabetes is concerned, and many patients who, under former conditions, were doomed to die in a comparatively short time, may now look forward to a life of health and activity. The marvellous success of insulin in the treatment of severe and otherwise hopeless cases of diabetes is one of the most striking triumphs in the whole field of modern therapeutics.

Preparation of Insulin.

Banting's early work on the isolation of insulin was based on the supposition that the trypsin of the pancreas destroyed the internal secretion, and that this accounted for the failure of previous investigators. It was well known to physiologists that the ordinary pancreatic tissue, which secretes trypsin and other enzymes, underwent degeneration after ligature of the pancreatic duct, while, on the other hand, the islets of Langerhans were apparently not affected. Banting, therefore, tied the pancreatic duct in an animal, and after degeneration of the pancreatic acini had taken place, removed the pancreas. Such a pancreas contained no enzyme, so that if the theory mentioned was correct, an extract containing active insulin ought to be obtained. This actually proved to be the case, and constituted the earliest experiment in a research destined to have the most far-reaching results in clinical medicine. Fortunately, however, it was soon found that initial tying of the pancreatic duct was unnecessary, for experiment showed that quite active preparations of insulin could be obtained from the normal

pancreas. It is, therefore, not quite certain whether Banting's original view is correct, but this is of little importance from a practical point of view. At any rate, the conception led to a great advance in medical treatment. There is no doubt that the discovery of insulin was facilitated very much by the use of modern methods of blood-sugar estimation, for it was essential in judging of the effect of the substance on animals that estimations of blood-sugar should be carried out at frequent intervals. Some years ago this was practically impossible, but now blood-sugar may be estimated in the same animal every few minutes if necessary. Taking everything into consideration, however, it still remains something of a mystery why insulin was not isolated many years ago.

The present method of preparation of this product is somewhat tedious and laborious, but the principle of its isolation depends on a process of fractional precipitation with alcohol of an extract of ox pancreas. By this means certain deleterious and irritating substances are left behind, and the insulin is ultimately obtained in a form more or less suitable for clinical purposes. Various methods for the further purification of this crude insulin are employed. In this country, treatment with picric acid with the formation of a picrate is carried out as an intermediate step, while, in America, precipitation at a given hydrogen-ion concentration of the solvent is the method which is most favoured. Quite recently Dodds has worked out a simple and expeditious method for the isolation of insulin. In this process the minced pancreas is thoroughly mixed with solid picric acid and the resulting insulin picrate isolated by extraction with acetone. The picrate so obtained is purified on the lines suggested by Dudley. In the preparation of insulin, great care has to be exercised to ensure that the product is sterile, for it is obvious that contamination of the pancreas by intestinal contents might result in infecting the patient. All these difficulties have now been overcome, and quite reliable insulin is being prepared

commercially in this and other countries. In this connection the thanks of the community are due to the Medical Research Council, who took steps to control and promote the manufacture of insulin in this country, with the result that the samples now being made here are reliable in strength and action. Were it not for the measures taken by the Medical Research Council, it is probable that the market would be flooded with useless preparations, and an excellent remedy might have fallen into disrepute.

Standardisation of Insulin Dosage.

The activity of insulin preparations is at present ascertained by means of rabbit experiments. The amount of insulin required to reduce the blood-sugar of a large starved rabbit to about 0·04 per cent. in two hours or so is adopted as the basis of unitage. Generally, when the blood-sugar reaches this level the animal goes into convulsions. The amount of insulin required to produce the above effect in a rabbit is equivalent to about 3 units, according to the nomenclature which at present obtains, and an ordinary human dose is taken as representing three to four times this amount, or about 10 units.* In many patients, of course, much larger doses may be given with impunity, while, in others, smaller doses may be sufficient. Unfortunately, different rabbits vary very much in their response to insulin, so that the method of standardisation just described is not a very accurate one. Patients also vary to a very great extent. It is important that all insulin preparations should be standardised as carefully as possible, so that the different samples on the market may all have approximately the same strength. On the other hand, extreme accuracy is at present impossible, and however desirable scientifically, is not absolutely essential for the clinical use of insulin. Indeed, the present standardisation seems quite efficient for all practical

* The insulin at present on the market is really somewhat stronger than is indicated by the above unitage.

purposes. Both American and British insulin are now put up in small phials with rubber caps to prevent the necessity of opening the bottle each time a dose is required. By this method bacterial contamination is avoided. The strength of the preparation is such that 1 c.c. of the liquid contains either 10 units or 20 units of insulin. For general purposes the preparation containing 20 units per c.c. is perhaps the most convenient.

Recently a preparation of insulin of double strength has been put on the market by Burroughs Wellcome and Co. Of this insulin, 1 c.c.=40 units. This preparation is exceedingly useful in the case of patients who require large doses, for the necessary amount of insulin can be given without having to inject too much bulk of liquid.

Symptoms produced by Insulin.

When the dose of insulin given to a patient is too large, various symptoms may be produced, and it is this action of insulin that has to be guarded against in the routine treatment of diabetic patients. The occurrence of these clinical phenomena is associated with the action of insulin in reducing the blood-sugar. When the blood-sugar gets too low, the fact is indicated by the appearance of these symptoms, but it is now certain that patients differ greatly as to the exact blood-sugar concentration that may be present when the symptoms come on. Taking the normal resting blood-sugar as about 0·1 per cent., it would seem that in certain subjects even a slight decrease to about 0·08 per cent. or so may be associated with insulin symptoms, while in others a blood-sugar as low as 0·05 per cent. may be present, and yet the patient may feel quite well. In a general way it is now established that the train of symptoms induced by insulin do not appear when the blood-sugar is normal or above this level, and that they are liable to manifest themselves whenever the blood-sugar sinks to a subnormal value; the exact level at which they appear depends on some unknown factors present in the patient. The association

of these insulin symptoms with a more or less lowered blood-sugar concentration—a hypoglycæmia—is, however, so pronounced that they are generally referred to as hypoglycæmic reactions. It may be taken for granted that, when insulin symptoms do come on, the lower the blood-sugar the more severe are the symptoms likely to be.

Symptoms of Insulin Hypoglycæmia.

The nature of these symptoms may vary, but they generally consist of flushing of the face, with sweating, often followed by some degree of pallor. The sweating may be very marked. There is sometimes a sense of constriction about the throat and chest. The patient feels giddy, and a marked sense of physical weakness may be present. The limbs are frequently cold, and occasionally the first feature observable is a blanching of the face. In other cases the initial symptom is a feeling of nervousness or distinct tremulousness, so that the patient finds it impossible to co-ordinate his movements; when he tries to write, for instance, he sprawls on the paper. Sometimes the symptoms may be entirely subjective, consisting of nervousness, a feeling of impending disaster which the patient cannot explain, or a sense of weakness coming on suddenly. In one of my patients, the only marked symptom present was excessive hunger about two hours after the injection of insulin. In children the pulse-rate is frequently accelerated.

If the condition is not relieved by the means to be described below, the nervous symptoms may become very marked, with intense anxiety and severe emotional disturbances. In very severe cases sensory and motor aphasia, delirium and confusion may all be observed, with collapse and syncope, which may finally result in a state of unconsciousness. Convulsions, so frequent in the hypoglycæmia of rabbits, do not appear to be common in man, though they sometimes occur. Marked increase of muscle tonus and a temporary cataleptic state may be

seen occasionally during the return of the patient to consciousness.

It will be observed that the predominating feature of insulin symptoms is their nervous character, and they must therefore be the result of some action on the nervous system. The explanation previously advanced was that the brain required a certain amount of sugar in its nutrient blood-supply, and that when this supply was diminished below a certain minimum these symptoms ensued. In the light of more recent knowledge this explanation is not valid, for though low blood-sugar undoubtedly plays a large part in the production of these phenomena, yet, as already indicated, other factors must obviously be operative as well.

Though the symptoms following insulin may be very varied and of all degrees of intensity, the hypoglycæmic condition can be easily recognised, and, in the majority of cases, is by no means severe. In my experience the chief symptoms complained of by patients are as follows:

1. Hot flushes, especially on the face.
2. Some slight weakness of the limbs, faintness and giddiness.
3. Sweating.
4. Tremulousness.
5. Vague objective symptoms of apprehension—*e.g.*, fear that some disaster is about to take place.
6. Coldness of the limbs.

If any symptoms of this kind supervene while a patient is having insulin, it may generally be assumed that the dose is too large and requires adjustment. The symptoms usually come on from one to three hours after insulin, but, not infrequently, they are observed from four to six hours, or even up to twelve hours, after injection. As an indication of the different effects of insulin on normal individuals, the following notes of an experiment carried out to test this point are interesting:

Two healthy medical men, each about the same build, age, and weight, were given 50 grams of sugar by mouth, and shortly afterwards 20 units of insulin were injected

hypodermically. For a day or so before the experiment both subjects took the same amount and the same kind of food. Subject A had no symptoms whatever after the insulin, while subject B had, on two occasions, symptoms so severe that it was difficult to get blood for sugar estimations. Fifty grams of glucose given by mouth had only a temporary effect in relieving these symptoms, and very soon the condition was as severe as before. A further 60 grams of glucose were then administered, with the result that the insulin phenomena passed over once again. The results are given in Table XII., p. 158. The marked difference in the two subjects is very striking.

Subject B described the symptoms he experienced in the following words: "The first noticeable symptom was profuse sweating of the face, scalp, and neck. This was very quickly followed by inability to perform fine movements with the hands, and weakness of the legs, which, however, was only noticed when standing up. General symptoms were dizziness and an impression as of all near objects being far away and having a swaying movement. On recovery after glucose, the sweating, dizziness, and swaying sensations were the first to go; the sense of weakness in the limbs remained for the longest time."

Treatment of Insulin Hypoglycæmia.

Though the symptoms of the hypoglycæmic complex may sometimes be very severe, it is fortunate that they respond very easily to treatment. Sugar given by the mouth will very quickly remove all symptoms, whether mild or severe, so that there is little or no danger associated with the use of insulin if the patient is very carefully warned to take sugar whenever any symptoms, such as those described, follow the injection.

Any kind of sugar will do, but glucose is perhaps best. Since it is advisable to get the sugar into the circulation as soon as possible, it is a good plan to keep a glucose solution (say 50 per cent. strength) handy, and to ask the patient to drink 1 to 2 ounces of this when symptoms

TABLE XII.

EFFECT OF INSULIN ON TWO NORMAL SUBJECTS.

Time.	*Subject A.*
10.3	Blood-sugar = 0·114 per cent.
10.22	50 grams sugar given.
10.30	20 units insulin given.
10.52	Blood-sugar 0·109 per cent. No symptoms.
11.7	„ 0·109 „ „
11.22	„ 0·095 „ „
11.37	„ 0·087 „ „
11.47	„ 0·114 „ „
11.57	„ 0·113 „ „
12.7	„ 0·102 „ „
12.17	„ 0·095 „ „
12.27	„ 0·100 „ „
12.37	„ 0·100 „ „
12.47	„ 0·100 „ „
12.57	„ 0·100 „ „

Time.	*Subject B.*
10.3	Blood-sugar = 0·114 per cent.
10.22	50 grams sugar given.
10.30	20 units insulin given.
10.52	Blood-sugar 0·109 per cent. No symptoms.
11.7	„ 0·07 „ „
11.22	**Symptoms marked.** 50 grams glucose given.
11.37	**Symptoms still present.**
11.47	Symptoms passed over.
11.57	Blood-sugar 0·128 per cent.
12.7	„ 0·132 „
12.17	„ 0·112 „
12.27	**Marked symptoms present.**
12.37	**Marked symptoms present.** 60 grams glucose given.
12.47	**Symptoms still present.**
12.57	Blood-sugar 0·129 per cent. No symptoms.

come on. This may be followed by another 2 ounces if the condition does not clear up in fifteen to twenty minutes. From the practical point of view, it is perhaps easier to use barley sugar; the patient is told to eat a stick or two of this when necessary. Patients on insulin should always

have some such carbohydrate as barley sugar at hand, so that they may take some whenever they feel the approach of symptoms. Though the patient may not perceive the onset of the first attack, he soon begins to recognise the very earliest symptoms in subsequent attacks; by taking sugar he can often prevent their further development.

When insulin is given carefully, no serious hypoglycæmic symptoms should ever ensue, but, obviously, if too large doses are injected, and the patient becomes unconscious, more drastic treatment is essential. One of the best means of combating the condition in the unconscious patient is the injection of 1 c.c. of a 1 in 1,000 solution of adrenalin. Generally, this results in a speedy return of the patient to consciousness, but, occasionally, when no glycogen is present in the tissues, adrenalin may fail. In all cases, it is safer to give sugar after adrenalin treatment. If the patient regains consciousness, the sugar can be given by mouth. If unconsciousness persists, glucose must be injected intravenously. From 100 to 200 c.c. of a 20 to 30 per cent. solution may be used. Subcutaneous injection of glucose into the loose tissue of the abdominal wall may be helpful if the facilities for intravenous injection are not at hand. Glucose may also be passed into the stomach by a tube, but this is frequently not a very easy proceeding in an unconscious patient. In any case, the important point is to get glucose into the blood-stream as quickly as possible. A dose of pituitrin (1 c.c.) given subcutaneously also produces good results. In cases of collapse, stimulants such as strychnine and camphor given hypodermically and hot coffee per rectum may be of great value. A hot drink after the recovery of consciousness seems to help the patient.

Though severe hypoglycæmic phenomena with unconsciousness were fairly often observed some time ago, when our knowledge of the action of insulin was very limited, they should never be encountered when the insulin treatment is carried out on the lines to be fully described below.

Effect of Insulin on the Diabetic Condition.

Insulin acts in tending to restore the diabetic patient to the condition of the normal individual. The therapeutic use of insulin results in a disappearance or marked reduction of the urinary sugar and ketone bodies. The excessive blood-sugar is also reduced towards the region of the normal level. In subjects whose diets are carefully correlated with the insulin dosage, the blood-sugar may often be kept within normal limits and the urine quite free from sugar and ketone bodies. Very careful adjustment of diet to insulin dosage is, however, required to produce this effect, and frequent modification both in diet and in insulin may sometimes be necessary. It may be taken as a general rule that insulin will produce no deleterious effects as long as glycosuria is present, so that it is easy and safe to regulate the dosage by examination of the urine for sugar. In the use of insulin, blood-sugar estimations are of great value, and should always be carried out when possible; but experience shows that they are not essential in the great majority of cases. When glycosuria disappears, examination of the urine does not help us any more, and it is at this stage that blood-sugar estimations are of most value, for without this means of ascertaining the blood-sugar content we are, to some extent, working in the dark. In some patients, also, sugar may disappear from the urine when the blood-sugar is still very high (even as high as 0·3 per cent. or more), and in such cases the only means of ascertaining the true position is by blood-sugar estimations. Generally, however, as indicated in Chapter II., the disappearance of glycosuria indicates that the blood-sugar is below 0·18 per cent. or so; if the urine continues to be persistently sugar-free, experience shows that the blood-sugar content is generally much lower than this, and frequently is found to be more or less normal. It seems to be much easier to reduce a high blood-sugar to the normal level than it is to reduce a normal blood-sugar to a state representing hypo-

glycæmia. One of the most striking features of insulin treatment is the rapidity with which some patients put on weight. Also, in many cases the ketosis rapidly diminishes, with the result that the patient feels much brighter and happier. The increase in strength and energy is very pronounced, and after a few weeks it frequently happens that the patient passes from a state of more or less helpless misery to one of comfort and health. Many patients with long-standing diabetes are able to resume work, and appear to be as fit as the average person. Though some cases of failure are reported, it is certain that the great majority of diabetic patients respond to insulin treatment in a wonderful manner.

The Type of Case in which Insulin is Indicated.

As a rule, there is little difficulty in coming to a conclusion as to the advisability or otherwise of using insulin in any given case. Frequently the terrific ravages of the diabetic condition are only too obvious, and in spite of long and careful dietetic treatment, the patient is reduced to a state of extreme helplessness and emaciation. He passes large amounts of urine, glycosuria is well marked, and large amounts of ketone bodies are passed. He complains of great physical weakness, and presents altogether a pitiable picture. In such patients it is clear that the end cannot be far off unless insulin is used, and no possible doubt as to its necessity can arise.

Other cases may give rise to greater difficulty in deciding whether insulin should be used. In this connection, a very common type of patient is the elderly individual who complains of being generally out of sorts, with weakness of the limbs, but who has few symptoms that could be definitely attributed to diabetes. Examination of the urine may show a large amount of sugar, but no ketone bodies, or at most only traces. There is, perhaps, no emaciation, and the patient may appear to be enjoying quite good health. Should we use insulin in a case of this kind? The answer is not always easy to give, but such

a condition, though apparently of no great importance as far as objective symptoms are concerned, should never be neglected. First of all, a careful dietetic régime should be ordered, but if this is not successful in removing the glycosuria and materially reducing the blood-sugar, insulin ought to be employed. In these patients there is not much danger of coma, and some of them live to quite an advanced old age; but the condition is so often associated at a later period with definite symptoms that it should always be taken seriously. The chief of these symptoms are:

1. Eye changes, often ending in blindness.
2. Neuritis of various degrees.
3. Intense local and general irritation.
4. Weakness of the limbs, and pains in the back and sides.
5. Diabetic gangrene.

Of these the most tragic is blindness. I have seen a great number of patients of this type who have been suffering from marked glycosuria and hyperglycæmia for many years and in whom the eyesight is now practically gone. Much can be done to prevent this calamity at an early stage of the disease, but once definite eye symptoms are established, they are very difficult indeed to treat. Neuritis also may be very troublesome, and sometimes local irritation is so extreme that the patient's life is rendered miserable. General weakness and severe cramp-like pains may also be present, while gangrene constitutes an important and dangerous complication. Though this type of persistent glycosuria may give rise to little or no trouble, it is impossible to foresee what is likely to happen in any particular patient, and the condition should be controlled if possible. Speaking generally, it is most important before using insulin to make certain that the case is really one of diabetes or very marked glycosuria with a high blood-sugar content. If the patient's urine does not give a definite ketone reaction with Rothera's test (p. 94), great care must be exercised, and the possibility of the case being one of renal glycosuria must never be over-

looked. In this condition it may be very dangerous indeed to treat a patient with insulin, since the blood-sugar may be already somewhat low. Renal glycosuria can be easily excluded by means of a sugar tolerance test carried out as described on p. 31, but, in many cases, this is not necessary, though in some it is imperative. Experience shows that in a large number of patients suffering from renal glycosuria the sugar is excreted only after meals, and this fact can be taken advantage of in deciding as to the nature of the case. A very simple method is to give the patient a dose of 50 grams or so of glucose dissolved in a little water, and get him to empty his bladder two and a half to three hours after the ingestion of the glucose. This specimen of urine will contain glucose, but a specimen passed after this time may not show any glycosuria. Instead of taking glucose, an ordinary meal rich in starchy materials may be eaten, and the urine tested in the same way. If sugar is not being passed in the urine three hours after a glucose or carbohydrate meal, the individual is not a suitable patient for insulin, and the condition is probably one of renal glycosuria. Of course, it is obvious that this test will not exclude all cases of renal leakage, for some patients suffering from glycosuria of renal origin pass sugar continuously. In my experience, however, this type is comparatively rare. In general, there are few or no symptoms associated with this renal condition. On the whole, it may be said that the urine of the average patient who requires insulin treatment will give marked reactions for "acetone" and "diacetic acid" in the urine, but this is not always so. Here it may be noted that acetone may be present in the urine of any patient, whether suffering from diabetes or not, if his diet has been recently changed to one containing a large amount of protein and fat with very little carbohydrate. If any real difficulty arises as to the suitability of a patient for insulin treatment, do a blood-sugar estimation, when the exact state of matters will be revealed. Enquire carefully into the history of the patient, and

ascertain whether he has lost weight. If he has not dieted before, and is found to be suffering from diabetes, try the effect of diet before giving insulin. In many cases diet will control the condition, at least for a time, and insulin may not be necessary. In young people, however, in whom the disease is often more or less acute and intense, it is perhaps advisable to give insulin in all cases, for this gives the best chance for the diseased pancreatic cells to regain some of their lost activity. Occasionally, one sees a patient with glycosuria who is rapidly wasting and going downhill, but on more detailed examination it is found that the amount of sugar in the urine is very small (often under 0·5 per cent.), with no acetone reaction, and that the blood-sugar is but little raised. In one patient of this type who was about to be treated with insulin, the blood and urine sugar was found to be so low that the condition could hardly be due to diabetes. Further examination revealed a malignant growth in the stomach. Careful attention to the various points mentioned will help us to decide whether insulin is indicated in any particular patient. In this connection, the estimation of blood-sugar is often of very great value and frequently settles the matter.

A Word of Warning.

When the general state of the patient is such as to suggest the need for insulin there are but few contra-indications to its use. There is, however, one condition in which insulin may give rise to tragic results. This condition is cardiac disease. While insulin may be safely given to patients suffering from ordinary valvular disease, its use is exceedingly dangerous when angina pectoris or marked cardiac degeneration is present. It is therefore necessary to exercise the greatest care when treating such patients. When necessary, insulin may be given, but the urine should not be rendered sugar-free, and no attempt should be made to keep the blood-sugar within

normal limits. The best plan in these patients is to give a fairly large allowance of carbohydrate with just sufficient insulin to control the symptoms without freeing the urine from sugar. The exact dose depends on the condition of the patient, but generally this should be small, though some patients with angina can stand fairly large amounts with safety. The great point is to keep the blood-sugar moderately high so as to prevent hypoglycæmic attacks. When the dose of insulin is too high, what apparently happens is that at some time or other the patient whose insulin dosage is sufficient to keep his urine free from sugar gets his blood-sugar reduced below the normal. This gives rise to a mild attack of hypoglycæmia, which in turn sets up an anginal attack. Angina pectoris developing as the result of hypoglycæmia is likely to be severe and often proves fatal.

It is therefore very important, especially in the case of elderly patients, to enquire carefully for any history of angina and to examine the heart before deciding on insulin treatment. In this connection it might be mentioned that the typical description of angina pectoris as given in the ordinary textbook is by no means a true picture of what we usually meet in actual practice. Often the pain is by no means severe, and unless questioned carefully the patient may not mention it. Investigation reveals the site of this pain together with its distribution and its relation to exertion and mental stress. Its nature will thus become obvious. It cannot be too strongly emphasised that these apparently trifling attacks of angina are just as likely to prove fatal during hypoglycæmia as are the well-marked classical attacks. Insulin can be given with safety in patients suffering from angina pectoris, but the amount of insulin must never be sufficiently great to induce any risk of an attack of hypoglycæmia. Many tragic results have followed the free use of insulin in such patients.

Some Observations on the Effect of Insulin in Diabetes.

As already mentioned, insulin restores the diabetic to a normal condition as long as a suitable dose of insulin is being administered. Insulin does not cure diabetes. To everyone who has had much experience of this disease it is but too obvious that the more severe types are essentially progressive in nature, and the Allen dietetic treatment, so largely used before the advent of insulin, never succeeded in doing more than postponing the fatal issue in such cases. No authority who has really taken any interest in the subject and watched patients over long periods has, as far as I know, ever expressed any other opinion. No doubt, the best chance for the pancreatic tissue to recover its efficiency is given when the blood-sugar is kept as nearly normal as possible, but the advocates of the theory that recovery of the pancreatic cells may occur when the blood-sugar is kept low have still to show that insulin produces better effects in this way than did careful dietetic treatment. So far, we have not had sufficient experience of insulin to enable us to make any dogmatic statements, but analogy with what happened in the past when the patients were on carefully restricted diet does not suggest a very rosy outlook. True, the employment of insulin enables us to control the course of the disease more effectively, and to keep the blood-sugar more or less within normal limits. It must not be forgotten, however, that we were frequently able to do this by the use of diet in the past, yet we failed to cure diabetes. No doubt, in some instances, when the diabetes was of a very severe and progressive type, it was impossible to control the patient's blood-sugar, so that there was no real chance given for recovery, but many diabetic patients, on the other hand, went on for a comparatively long time with normal blood-sugar values, and taking a diet that was amply sufficient for all purposes. This treatment never cured the condition, and the story was almost invariably a return of sugar in the urine sooner or later, which necessitated

an ever-increasing curtailment of diet. In this connection Banting remarks that when the production of insulin by the pancreas falls below a certain minimum, no dietetic treatment will stay the progress of the disease. It is most improbable that insulin will have any more permanent effect in *curing* the disease than dietetic means. It is, of course, too early to make definite statements on this point, and our aim in treatment should be to ensure, if possible, that the blood-sugar content should be normal. In this we are only following the ideals aimed at in the Allen treatment. Unfortunately, all my experience so far goes to suggest that insulin will have to be taken permanently to relieve the symptoms in cases of severe and long-standing diabetes, just as thyroid extract must be taken in myxœdema. I have seen a few acute cases where the initial severe symptoms were tided over by means of insulin, and the patients later on remained free from glycosuria on very small doses of insulin, or even without any insulin. Such results, however, could no doubt be obtained by judicious dieting, and need not necessarily be put down to any special effect of the insulin. The important part played by insulin in such cases is that it enables the patient to recover from the earlier symptoms, which may occasionally be of the nature of coma; in such cases, no initial dietetic treatment would be likely to prove successful. While it is our duty when using insulin to keep the patient as normal as possible with regard to his blood-sugar, it is my opinion, based on experience of a comparatively large number of cases, that insulin will do no more to cure diabetes in the adult than does thyroid extract to cure myxœdema. In the young, however, an interesting question arises. Definite evidence has been brought forward that regeneration of the islet cells of the pancreas may take place in a young diabetic when the disease is controlled by insulin. From this it might be argued that the administration of insulin in very young people might sometimes effect a cure by allowing new pancreatic cells to develop. Several of my cases

now require much smaller doses of insulin than they did at the earlier stages of treatment, but I have not yet seen a single patient whose recovery of tolerance was sufficiently marked to enable him to discard insulin. In some of these young patients there has been no sign of increased tolerance, and the amount of insulin had sometimes to be increased as the child grew older. It seems fairly certain that all these children will find it necessary to continue the administration of insulin throughout life. It is quite certain that the lives of many children who would otherwise die of diabetic coma can be saved by insulin, and that the outlook is not necessarily as black as it is sometimes considered to be. Given a child otherwise healthy, there is really good ground for the view that such a child may reach adult life, and be no worse off than the average patient in whom diabetes first showed itself at a much later stage in life.

General Directions for Treatment with Insulin.

Having ascertained that the particular patient to be treated is a suitable case for insulin, the next point is to arrange a diet and to give the patient the necessary amount of insulin to keep his urine sugar-free, and, if possible, to keep his blood-sugar within normal limits. The nearer the blood-sugar content is to 0·1 per cent. the better, but variations from this amount to 0·14 or 0·15 per cent. are constantly taking place in the normal individual, and such variations are also likely to occur in patients under treatment. A blood-sugar varying from 0·09 per cent. to about 0·14 per cent. may be considered satisfactory. Frequently it is easy to produce this effect, at other times it is difficult, and occasionally it is practically impossible. In very severe cases, it is sometimes found that the amount of insulin necessary to keep the urine sugar-free, even when a minimum diet is prescribed, is so excessive as to be quite beyond the financial means of the patient. Under such circumstances, the patient, though perhaps passing a certain amount of sugar, does quite well, as a rule,

as long as insulin is being administered. Here, the practical aspect of the question has to be separated from purely theoretical considerations, and it is better to give the patient a moderately good diet with the maximum amount of insulin, even when such diet produces glycosuria, rather than keep him on a starvation diet on which the glycosuria may be much less or even occasionally absent. In patients suffering from this severe type of diabetes, experience over long periods goes to show, as already suggested, that increased tolerance for carbohydrate is not likely to result, and it is, therefore, best to let the patient go on in comparative comfort, rather than subject him indefinitely to conditions of severity amounting almost to torment without any reasonable chance of deriving corresponding benefits from them.

Diets of a most unappetising nature, consisting chiefly of one or two substances such as vegetables and fat, for instance, are sometimes given, so that, as far as food is concerned, the last state of the unhappy patient is worse than the first. For short periods such diets may be suitable, and help materially in eliminating glycosuria, though marked ketosis may be present. Generally, however, they are quite unnecessary, and possess the drawback that patients will not carry on with them for any length of time. Now, in order that the best effects should be obtained from insulin, it is essential that the diet and dose of insulin should be carefully correlated, and the best means of achieving this happy combination is the problem that confronts us in every case we treat. Several different methods have been suggested, but the simplest and most satisfactory in the end is for the medical man to put his patient on to a fixed diet which he calculates will be sufficient in all respects, and then to give increasing doses of insulin until satisfactory results are obtained. A suitable diet may be built up on the lines suggested in Chapter VIII. Roughly, the daily dietetic allowance should contain from ten to fifteen calories for every pound the patient weighs. The exact quantity given will naturally depend

on various circumstances, such as the amount of work the patient is performing and other factors. The protein allowance should be in the neighbourhood of ½ gram or less per pound weight of the patient, while the carbohydrate should be small and the fat content comparatively high. Approximately, the carbohydrate content should not exceed about one-third of the weight of the fat given. Though in certain patients it may occasionally be inadvisable to give carbohydrate as starch in the diet, yet, for various reasons, it ought to be given when possible. It ensures safety in the use of insulin, especially during the earlier stages of treatment, and makes the diet more palatable. Again, there is a good deal of evidence that carbohydrate is more effectively dealt with by insulin than is the sugar derived from protein. In this connection it should be remembered that about 60 per cent. of the weight of protein material goes to form sugar in the body, so that total withdrawal of carbohydrate from the food has not very much to support it from the practical point of view. If carbohydrate in the form of starchy food (*e.g.*, bread) is employed, it should be given in the meals following the insulin injections; as little carbohydrate as possible should be given in the intervening meals.

Within recent times, American observers have worked out certain more or less elaborate scientific methods for building up a suitable diet for any particular patient. These methods depend on a knowledge of the so-called "basal metabolism" needs of the patient. They are interesting and useful, but, unfortunately, all patients do not react in exactly the same way, and some subjects appear to be beyond the control of mathematical formulæ. The various tables and curves used in modern work are of great scientific interest from the point of view of the specialist, but for the medical man who treats an occasional case of diabetes they are superfluous. Mathematics is not always an exact science when applied to clinical medicine, though it undoubtedly has its place in this field; that place must always be subordinate to common sense.

Examples of Diets suitable for Insulin Treatment.

Though it is an easy matter to build up a diet suitable for the needs of any patient by the use of the table given on p. 130, some medical men find the process a difficult one. From the practical point of view it is certainly more convenient to employ some kind of standard diet, and though, theoretically, each patient may require somewhat different quantities of food, yet in practice it is found quite possible to treat patients by the use of one or two specimen diets. The following diets are given as suitable for treatment with insulin, and may be employed with satisfactory results in the great majority of cases. During the treatment they may require modification according to the needs and progress of the patient. Whether diet No. 1 or No. 2 is chosen will depend on the conditions and the general severity of the symptoms. It must be remembered that the use of diets containing too little nourishment for the patient's needs will simply result in a destruction of the patient's own tissues, so that the menu employed must contain sufficient calories. Also, it is sometimes forgotten that a very artificial diet may result in a disappearance of glycosuria, but large amounts of ketone bodies may be present in the urine. Ketonuria, especially when well marked, is probably a much worse feature than glycosuria. The two diets given are suitable for adult patients of average weight (140 to 160 pounds). For children smaller amounts must be given, depending on the age and other factors, as already indicated in Chapter VIII.

No. 1 Diet.

This diet is found to answer well in a diabetic patient whose symptoms are not very severe, though dietetic measures fail to control the condition. The results obtained are quite good, but, as described later, distinct modifications may be necessary from time to time. The effect of treatment is indicated by the condition of the urine as regards sugar and ketone bodies, and by the

DIET NO. 1.

For Moderately Severe Cases of Diabetes.

	Carbo-hydrate.	*Fat.*	*Protein.*	*Calories*
Breakfast (9.30 *a.m.*) :				
2 ounces bacon 1 egg 1 ounce white bread ½ ounce butter ½ ounce thick cream 4 ounces vegetables (Group A)	19·5	63·5	14·5	732
Lunch (1 *p.m.*) :				
Beef tea 4 ounces white fish ½ ounce Callard's starch-free bread ½ ounce butter ½ ounce cheese 1 ounce thin cream 2 ounces vegetables	3	25	30	366
Tea (4 *p.m.*) :				
Tea ½ ounce thin cream ½ ounce kalari biscuit (Callard) ½ ounce butter	1	20	6·5	222·5
Dinner (6.30 *p.m.*) :				
Clear soup 4 ounces meat 1 ounce bread ½ ounce thick cream ½ ounce cheese ½ ounce butter 4 ounces vegetables Coffee	19·5	38·5	30·5	561
Total ..	43·0	147	81·5	1,881

DIET NO. 2.

FOR VERY SEVERE CASES OF DIABETES.

	Carbo-hydrate.	*Fat.*	*Protein.*	*Calories.*
Breakfast (9.30 *a.m.*) :				
Tea, coffee, or beef tea ½ ounce thick cream 2½ ounces ox tongue 1 egg ½ ounce starch-free bread (Callard's or Allenbury's) 1 ounce butter 4 ounces green vegetables (Group A)	4·5	49	26·5	573
Lunch (1 *p.m.*) :				
Beef tea or bovril 2 ounces white fish (any kind) ½ ounce starch-free bread 1 ounce thick cream 1 ounce butter 5 ounces green vegetables	6	46	16	504
Tea (4 *p.m.*) :				
Tea ½ ounce thick cream ½ ounce kalari biscuits (Callard's) ½ ounce butter 2 ounces vegetables	3·0	27	7	293
Dinner (6.30 *p.m.*) :				
Clear soup 4 ounces meat (any kind) 4 ounces vegetables ½ ounce starch-free bread ½ ounce cheese 1 ounce butter Coffee	4	42·5	33	539
Total ..	17·5	164·5	82·5	1,909

general clinical improvement of the patient. Very thin patients should always show an increase of weight on insulin treatment.

No. 2 Diet.

In this diet no ordinary bread is allowed, so that the carbohydrate content is very considerably reduced. Patients, however, require some form of bread to enable them to eat up their butter, and a starch-free variety must be used. For this purpose Allen and Hanbury's diabetic flour is useful, since it contains no carbohydrate, and may be made into suitable bread in the patient's home. Special recipes for the baking of various kinds of bread are supplied with the flour. A special bread made with white of egg added to the flour is suitable for the present diet. It is prepared as follows:

Recipe for Bread prepared from Starch-free Flour.

Beat the whites of three eggs thoroughly, then gradually add in the contents of one packet of " Allenbury's " diabetic flour. Mix well. Place in a well-buttered tin and bake in a moderate oven for twenty to twenty-five minutes.

Instead of the above, Callard's casoid bread may be used. Callard's kalari biscuits also serve a useful purpose in such diets.

In Diet No. 2 the $2\frac{1}{2}$ ounces ox tongue given at breakfast may be substituted by 2 ounces meat, or $1\frac{1}{2}$ ounces sardines, or $2\frac{1}{2}$ ounces fresh herring (or mackerel), or 1 ounce bacon. For " meat " at dinner, any kind of meat may be used, such as mutton, beef, veal, chicken, fowl of any kind, venison, hare, or other game.

These diets are given only as indications of the lines to be adopted, and they may require modification according to circumstances. Thus, if a patient is passing a very large amount of sugar it may be advisable to begin with No. 1 diet, but to give only one-half or one-quarter the amount of white bread allowed in this diet. In very severe

cases, it may often be best to start off with No. 2 diet. Suitable diets for children may be arrived at by cutting down somewhat the amount of material in the specimen diets given here. As far as safety is concerned, it is best, in all cases, to begin with No. 1 diet, and unless the supervision of the patient is good, this course is to be recommended. Obviously, no very definite rules can be given, for the plan of treatment must vary with circumstances. The use of a diet containing a fair amount of carbohydrate may entail a longer period of treatment before the patient's urine is sugar-free, but, in the end, it often saves time. At any rate, we must begin with some type of diet, and it does not matter very much what particular one we adopt provided it is generally suitable and built up on correct principles. Our aim is to correlate diet with insulin dosage, and it is frequently necessary to modify the diet during treatment in order to attain this end; this can always be done with safety if the instructions given here are followed.

After-Treatment with Diet.

After the preliminary treatment is over the patient will have to continue with a modified diet. This of necessity must, after a time, be left in his own hands, and sometimes he finds it difficult to follow instructions. Though it is advisable to weigh the diet to begin with, it is usually quite unnecessary to continue with this practice. Experience shows that provided sufficient insulin is taken there are fair limits of diet between which the patient can live and thrive. Many of our accepted ideas with regard to diet are theoretical, and some of them do not always work out well in actual practice. In a case of diabetes of average severity it is quite possible for a patient to get along quite satisfactorily without weighing his food. Patients who are feeling fit as the result of insulin treatment are usually engaged in some business or manual labour and they cannot be expected to carry a balance about with them. Further, the mere idea of

having to weigh the food is frequently most irritating to the patient, as it constantly serves to impress upon him the fact that he is very different from other individuals. The best results are obtained with insulin when the patient leads an apparently normal life without undue worries or petty restrictions, and he should not be subjected to any conditions that are not absolutely essential. As the result of my experience during the last few years I have found that it is seldom if ever necessary to weigh the food if the patient is at all intelligent. Once the diet is settled by the medical man, all that is required is to teach the patient how much food is represented by a given weight. After a very little practice he is able to select and gauge his diet with ease. The average patient very soon learns to eat approximately the same amount of food each day without weighing it. If he makes a mistake now and then it does him little if any harm. I am of opinion that the added comfort induced by this method results in the patient being in better condition mentally and physically than is the case when his food is scrupulously weighed out. The simpler we make all the arrangements connected with insulin therapy the better results we obtain, provided that the main principles are always kept in view. The results of experience suggest that scrupulous weighing out of the diet to fractions of a gram, as is so often done, is quite an unnecessary ritual; it does no good and inflicts much hardship on the unfortunate patient. Gradually in all countries a tendency to make diabetic dieting as simple a process as possible is becoming manifest, and the common sense of this practice is being widely recognised.

Detailed Suggestions for Treatment of a Patient with Insulin.

Having determined that the case is a suitable one for the use of insulin, the first thing to do is to choose a suitable diet. If the symptoms are very severe, we may with ad-

vantage put the patient on to No. 2 diet at once; but if this diet is used it may be advisable to give it for a few days without insulin, and then to ascertain roughly how much sugar the patient passes per day while on this restricted régime. From his observation, it may be possible to get some idea of the daily amount of insulin that will probably be required, since 1 unit of insulin "looks after" about 2 grams of sugar. It must, however, be acknowledged that this figure varies very much indeed both in different patients and probably in the same patient at different times; no great reliance can, therefore, be placed upon this value for practical purposes, but it serves as a rough general guide. Another advantage in keeping the patient on this restricted diet for a few days before giving insulin is that it helps to ensure safety, for, if a patient persists in passing a fair amount of sugar on this diet, it is another indication that insulin is probably necessary, and that its administration will not be likely to cause any trouble. As already mentioned, if the patient is not under careful supervision it is certainly safer in all cases to begin with a diet on the lines of No. 1.

Having decided what diet is to be given, the patient is warned that certain symptoms may come on as the result of the insulin injections; he is told that these symptoms are generally not at all severe, and that they can always be removed almost immediately by taking sugar. The nature of the symptoms is carefully explained to him (p. 154), and an assurance given that, with the method of administration used in his case, any symptoms coming on will be, of necessity, very slight. Some sticks of barley sugar are procured, and very definite instructions are given that 1 or 2 ounces of this sugar are to be eaten whenever any symptoms of the nature described come on. This barley sugar is always kept within reach of the patient or on his person, so that he can procure some at any moment. In this connection, experience shows that excessive emphasis should not be placed on these symptoms as far as the instructions to the patient are concerned, for

sometimes a highly strung diabetic will imagine that he has insulin symptoms, and take large amounts of sugar, when his blood-sugar is still very high and he is passing large amounts of sugar in the urine. Under such circumstances, patients may do harm to themselves and retard the effects of treatment. It will, of course, be remembered that insulin symptoms never come on when the blood-sugar is high.

For the first week or ten days the patient should be kept indoors, although it is seldom necessary for him to be in bed. Arrangements are made to collect the urine passed during each twenty-four hours, and from an analysis of a sample of this the total amount of sugar passed per day is estimated. Qualitative tests for ketone bodies are also made (see p. 94).

Injections of insulin are then begun, and with the patient taking the same diet day after day the amount of insulin is *slowly* increased until the urine becomes free from sugar, or until a comparatively large dose of insulin is reached. It is best to begin with small doses (say 5 units twice a day), and, if possible, not to exceed a dose of 25 units twice daily as a maximum; indeed, great efforts should be made to arrange matters so that, if at all practicable, a smaller dose should suffice. The principle of the method of treatment advocated here is *to begin with small doses and to increase the amount gradually until the glycosuria disappears*, or until a dose is reached beyond which the medical attendant does not wish to go. This method ensures that if symptoms do supervene they are never severe or dangerous, for under these conditions it is obviously impossible for the patient to get a dose at any one time that is much in excess of his actual requirements.

The insulin is given twice a day by injection about thirty minutes or so before the morning and evening meals. Sometimes more frequent injections are given, but, generally speaking, this is inconvenient for all concerned. In bad cases it is generally quite safe to begin with 10 units twice a day, but, to be on the safe side, 5 units

had better be used to start with, unless it is quite certain that the patient is really suffering from a bad condition, and the supervision is good. As long as glycosuria persists, gradually increasing doses as indicated below may be given.

Suggested Doses of Insulin in Units.

	Morning.	*Evening.*
1st day	5	5
2nd ,, ...	5	5
3rd ,, ...	8	5
4th ,, ...	8	8
5th ,, ...	8	8
6th ,, ...	8	8
7th ,, ...	10	8
8th ,, ...	10	10
9th ,, ...	10	10
10th ,, ...	10	10
11th ,, ...	12	10
12th ,, ...	12	12
13th ,, ...	12	12
14th ,, ...	15	12
15th ,, ...	15	15
16th ,, ...	15	15
17th ,, ...	15	15
18th ,, ...	15	15
19th ,, ...	18	15
20th ,, ...	18	18
21st ,, ...	20	20
22nd ,, ...	20	20
23rd ,, ...	22	20
24th ,, ...	22	22
25th ,, ...	25	25
26th ,, ...	25	25
27th ,, ...	30	30

If after 30 units are given twice daily glycosuria still persists, it is best to continue for a time with this dose, and to cut down gradually the carbohydrate of the diet if the diet contains carbohydrate, or, if not, the protein may have to be reduced. If a carbohydrate containing diet such as No. 1 is used to begin with, it is much better practice to begin to eliminate part of the carbohydrate whenever it becomes obvious that a dose of 15 units or so of insulin twice daily does not render the urine sugar-free,

and not to increase the dose beyond this until the whole of the carbohydrate is, if necessary, eliminated from the diet. If after this is done the urine still contains sugar, the dose of insulin must be gradually increased; if necessary, still further modification of the diet as regards its protein constituents may be advisable. If in spite of a suitable carbohydrate-free diet the patient still passes sugar on a dose of 25 or 30 units of insulin twice daily, it is, in my opinion, better to let him go on passing some sugar in the urine, for such a case must be so severe that little chance of regeneration of the pancreatic cells remains. In the majority of diabetic patients it is possible, by suitable arrangement of the diet, to control the glycosuria when the patient is on a dose of from 15 to 20 units of insulin twice daily. When the patient no longer passes sugar in the urine, this generally means that the blood-sugar has been reduced to a level somewhat below 0·18 per cent. or so. Since no insulin symptoms come on until the blood-sugar sinks to below 0·1 per cent., there is a good deal of "buffer" sugar, so to speak, between the point at which glycosuria disappears and the point at which insulin symptoms ensue. It, therefore, frequently happens that the patient will stand a larger dose of insulin than the minimum required to make his urine sugar-free. It is when glycosuria disappears that the medical man is puzzled as to what he ought to do next. Should he decrease the dose of insulin slightly or increase the carbohydrate of the food? The best plan is to continue for a few days on the same diet and dose of insulin as were being given when the urine became sugar-free, and then, unless insulin symptoms are present, to increase the insulin *very slowly and by very small additions* (say by 1 to 2 units every two days) until very slight symptoms appear. At this stage the blood-sugar is below 0·1 per cent., and at this point the dose may be very slightly reduced or a little extra carbohydrate or protein added to the diet. By this means, it is generally possible to arrive at a dosage of insulin that will keep the patient's

blood-sugar within normal limits and his urine free from sugar.

When the directions given are carefully followed out, insulin can be given without a single blood-sugar estimation, though in all circumstances it is advisable to estimate the blood-sugar from time to time if at all possible. It is always very helpful to know what the state of the blood-sugar really is when glycosuria disappears, and though this can usually be ascertained by the onset of slight symptoms, there are some patients in whom insulin does not produce symptoms unless the dose is much increased over that which renders them aglycosuric. In such patients, it may be taken for granted that 5 to 10 units per day over and above that which resulted in freeing the urine from sugar will be sufficient to keep the blood-sugar within normal limits.

The exact graduated doses of insulin employed in the treatment of a case need not, of course, be those indicated above. The great point is to *go slowly, and the increase of insulin may be much more gradual even than that suggested in the table. It frequently happens that a patient on a given diet and dose of insulin may, at an early stage of the treatment, be passing large amounts of sugar, and yet, though kept on exactly the same diet and the same amount of insulin, may cease to pass sugar after a few weeks.*

It is, therefore, always best, in my opinion, not to increase the insulin dosage too rapidly. The giving of excessively large doses in the hope of rapidly rendering a patient sugar-free may result in tragedy, and is certainly an unsafe procedure. This practice explains those statements one sometimes finds in the literature, to the effect that a patient who required perhaps 70 or 80 units of insulin per day at an early period of his treatment, required, at a later time, only 20 to 30 units or less. The fact is that the large doses ought not to have been given at all in such cases, for equally good results could have been more safely and economically obtained with small doses given over a fairly long period. The idea sometimes put

forward that excessively large doses help to increase the sugar tolerance by keeping the blood-sugar at a low concentration for some time is obviously disproved by the fact that the same result can be obtained with low doses insufficient to lower the blood-sugar rapidly. In such cases, the patient's blood-sugar gradually decreases, and yet his tolerance gradually changes, so that his power to deal with carbohydrate is quite as good as it would be if his blood-sugar had been kept at a low level for some time by means of excessive doses of insulin.

The above suggestions for the use of insulin admit of many variations according to circumstances, but the broad principle put forward involves the use of graduated dosage increased very slowly. This is undoubtedly one of the most important points in the treatment of diabetes by insulin.

Some Observations on the After-Results of Insulin Treatment.

So far as our present experience goes, it would seem that insulin must be given permanently in the great majority of cases of severe diabetes. When this is done, patients do well, as a rule, but some subjects undoubtedly require larger doses as time goes on, so that constant increases in the amount of insulin are necessary if the urine is to be kept sugar-free. Some of these patients perhaps develop a certain amount of tolerance to the insulin quite apart from their diabetic condition, so that larger doses are required to produce the necessary effects. This condition is well seen in normal rabbits used for standardisation purposes. On the other hand, the increased dosage necessary may indicate a progressive deterioration of the patient's power to deal with carbohydrate; in other words, insulin has failed to stay the course of the disease.

It is frequently very difficult to keep a patient sugar-free for a long period, for many factors play a pronounced part in affecting the efficiency of a given dosage of insulin.

Thus, some patients require a larger dose in cold weather than in summer. A slight febrile attack, an ordinary cold, so-called influenza, a mild gastric disturbance, or almost any deviation from normal health may, in certain patients, give rise to marked glycosuria even when the patient is on the same diet and the same dose of insulin as was formerly sufficient to keep him sugar-free. The use of gas for removal of a tooth may cause a similar disturbance. Patients suffering from carbuncles or other features associated with a moderate or high temperature frequently respond very badly to insulin, especially when given in ordinary doses. This has also been my experience in cases of diabetic gangrene with toxic symptoms.

Sometimes patients exhibit marked temporary glycosuria and rise in blood-sugar without any ascertainable cause, so that it is necessary to appreciate the fact that it may be by no means easy to keep certain patients on a suitable dose of insulin for long periods unless they are subject to fairly constant supervision. Once a suitable diet and dose of insulin are found for any given patient, he generally goes on successfully for a considerable period, but at any time this particular dosage may require modification.

It is most important to appreciate the rapidity with which a patient on insulin may exhibit marked toxic symptoms, and even pass into diabetic coma as the result of some trifling ailment. When this happens, very much increased doses of insulin must always be used. On recovery, such patients generally require a greater daily amount of insulin than was necessary before; the most suitable dose may, for a time, not be very easy to ascertain, but usually a satisfactory arrangement can be arrived at. These upsets are apparently much more common in the winter and spring months, when infections of various kinds are so prevalent. In some cases of this nature, heroic doses of insulin may sometimes be necessary. In one diabetic patient under my care the urine was rendered sugar-free by insulin, and the

blood-sugar reduced to a concentration varying from 0·13 to 0·18 per cent.; this satisfactory state of affairs, which continued uninterruptedly for many months, was obtained by the administration of 20 units of insulin twice daily. After about nine months' treatment the patient suddenly complained of being slightly nauseated and tired; he slept badly that night, and on the following day passed into deep coma with very marked "air hunger" and a greatly accelerated pulse. It was necessary to inject 190 units of insulin within six hours in order to relieve the condition. The patient recovered, and is now sugar-free on 25 units of insulin given twice a day.

Very frequently, after surgical procedures, the amount of insulin required, at any rate for some time, may be very much greater than before.

In the four years that have elapsed since insulin became generally available for the treatment of diabetes 291 patients suffering from typical diabetes have been treated in a special clinic in the Medical Unit of St. Thomas's Hospital. All these patients showed definite ketosis, and the majority of them were young or middle-aged. Cases of ordinary glycosuria without ketosis are not included in this list. Each patient was first treated as an in-patient in the ward, the diet and insulin dosage being carefully worked out. After being discharged from the ward the patient attended the clinic at definite intervals. As an outside patient he was usually being looked after by his medical practitioner. When any change in diet or in insulin dosage was considered advisable, the practitioner was informed of the result of the examination, and the suggested changes indicated to him. The complete treatment of the case, however, was, as far as possible, controlled by the special clinic. The figures on p. 185 show the results of insulin treatment of these cases up to date. In this connection I should like to thank Dr. Crozier of the Medical Unit for his help in keeping records of these cases and for assisting me in compiling the results.

Year of Admission of Patient.	*No. of Patients Admitted.*	*No. of Deaths to Date.*
1923–24	77	5
1924–25	76	2
1925–26	68	3
1926–27	70	2
Total	291	12

Several of these patients were admitted in coma, three of them developed coma on three different occasions, and a few more were in coma on two occasions. All these patients are now doing well. Two patients with tubercle bacilli in their sputum are still alive and in fairly good health.

Of the twelve deaths, one, a girl of nineteen, developed coma outside, and was treated by her local doctor. Another was treated in hospital, but was admitted at a rather late stage, and though apparently a case of uncomplicated diabetic coma, she failed to respond to insulin. Three of these cases recovered from coma, but died of cardiac failure. In all the others coma developed as the result of some such complication as influenza, pneumonia, or septic lesion.

These figures show a death-rate of almost exactly 4 per cent. As they were all well-marked cases, the figures indicate a very extraordinary improvement over the results of dietetic treatment. Judging from the death-rate prior to the use of insulin, the average number of deaths in these 291 patients would have been much greater if treatment had been restricted to diet alone. While it is quite impossible to give anything like exact figures, it is nevertheless possible to arrive at some probable conclusions as to what would have happened if no insulin had been used in these cases.

If we take six years as the average duration of life on diet alone, it appears that of the 77 patients admitted in 1923-24 at least half of them would now be dead. Taking everything into consideration, it seems probable that more than one-third of the total number of these 291 cases would

not be alive now. In addition to the above patients, I have seen a fair number regarding whom I have no definite statistics. The general impression conveyed, however, is that the average results of insulin treatment were somewhat similar. So far, I have only seen one diabetic patient who failed entirely to respond to insulin administration. As no post-mortem examination took place in this case it is possible that some other complication was present.

These results are only given as a general indication of what insulin can do for diabetes. They appear to be rather better than the average results of other observers, but this is probably merely an accidental occurrence, dependent on the fact that the comparatively small number of patients treated, as viewed from the statistical point of view, happened to be a fairly healthy sample in other respects. The figures point definitely to the conclusion that practically all uncomplicated cases of diabetes in young or middle-aged people can be controlled by the judicious use of insulin. It must also be remembered that the general physical condition of diabetic patients treated by insulin is altogether different from that which obtained under dietetic treatment. In many cases dietetic treatment was so severe that the patients could not be induced to continue with it. Some of them quite frankly stated that they preferred death to the physical agony which they endured. In almost all bad cases the period of a year or so preceding death was usually most distressing and hopeless. Now all is changed. The disease which was formerly so grave has been shorn of many of its terrors, and, in my opinion, it ought to be possible to control any ordinary case of uncomplicated diabetes and to restore the patient to a fair degree of health and comfort.

The Results of Insulin Therapy in Young Children.

It is well recognised that diabetes in the child is a very serious condition, and, in the absence of insulin, is liable

to prove fatal in a very short time. On the other hand, the disease is usually well controlled by insulin when a sufficient dose is given. Since nearly all children contract some of the various ailments common to children at some time or other, it is obvious that in the case of very young people there are special difficulties and dangers to contend with. In my experience, however, these dangers are not necessarily so formidable as they might appear to be. Undoubtedly very great care is necessary, and the dose of insulin must at once be increased when the onset of any of these ailments is accompanied by an increase in the diabetic symptoms. When this is carefully done the results on the whole are good. I cannot claim to have seen very many cases of diabetes in young children, but since 1923 I have treated over thirty children varying in age from two and a half to ten years, and all of these are alive to-day and in quite good health. We have not had a single death from diabetic coma in a child under ten years of age. Many of these children were first seen while in coma, and a few of them developed coma on at least two subsequent occasions. Some of them have contracted and safely weathered such conditions as whooping-cough, measles, and chicken-pox. While it must be admitted that the outlook from the theoretical point of view is not good in the case of children, practical experience suggests that the young diabetic can very often be safely guided through the storms which are peculiar to childhood, and that very satisfactory results can often be obtained.

Insulin in Elderly and Old Patients.

In old patients, as already indicated, true progressive diabetes with ketosis is not very common, though it is certainly met with from time to time. By far the most frequent condition in these patients is the type of glycosuria already discussed. In an uncomplicated case of diabetes in an elderly patient insulin appears to act as well as it does in the young or middle-aged, but, unfortunately,

it often happens that other ailments are present. In these circumstances good results could hardly be expected in general from the use of insulin in old patients, and this is in accordance with experience. Insulin, however, often gives excellent results in many old people who have glycosuria with such symptoms as weakness, neuritis, and local irritation, but whose condition is otherwise good. It all depends whether the lesion is or is not complicated with degenerative diseases, and other changes incident to old age. There is obviously an absence of the recuperative power of the young individual, and allowances must be made for this.

The Use of Insulin in Surgical Conditions Complicating Diabetes.

Insulin has revolutionised diabetic surgery. Before insulin was available the surgeon hesitated as a rule to incur the grave risk associated with an operation on a diabetic patient. In desperate cases, when an operation had to be attempted, coma often supervened and the patient died. Since insulin has become available for the treatment of these patients it is safe to say that, under good conditions, and when treated by someone who understands the use of insulin, the diabetic has about as good a chance as a normal patient who undergoes an operation. This is well borne out by the statistics of the Mayo Clinic. In 667 operations performed on diabetic patients only twenty deaths occurred. Taking into consideration the fact that many of these patients were suffering from arterio-sclerosis and other degenerative lesions, the results appear to be very satisfactory.

Some Anomalous Statistical Results.

From the excellent results obtained by the use of insulin it might be thought that diabetes would figure no longer in official statistics as an important cause of death. At any rate, it might be considered that the number of deaths

officially returned as caused by diabetes would be much reduced, and that this reduction would continue for several years. Since the majority of diabetic patients develop the disease when comparatively young, the natural inference would be that the lives of these patients would be prolonged for many years by insulin; ultimately, when death took place in the usual course of events, though the patient might die of something quite different from diabetes, there would be a tendency on the part of the medical man to return the cause of death as diabetes. Theoretically, then, there should be a marked diminution in the number of deaths from diabetes for several years, while after a certain period an increase might be looked for, but the majority of these deaths should be those of elderly people.

So far as official statistics go, however, insulin has apparently not decreased the number of deaths from diabetes. According to these returns, insulin has failed to affect to any material extent the death-rate from diabetes. We are therefore faced with the curious result that apparently the number of patients dying from diabetes is as high as ever, in spite of the undisputed fact that many lives are saved by insulin ? What is the explanation of this ? One possible explanation might be that the incidence of diabetes has largely increased during the last few years, and that, despite the beneficial action of insulin, the increase of the disease is so marked as to keep the death-rate up to the old level. This view really means that in the absence of insulin the death-rate from diabetes would be very materially higher than it now is. Against this view is the fact that insulin is such a potent measure in the treatment of uncomplicated diabetes that even a marked increase in the incidence of the disease should not materially increase the death-rate. There appears to be some evidence pointing to the conclusion that there is a tendency for some slight increase in the number of diabetic cases, but this does not explain the difficulty.

An examination of the age of death reveals the fact that the *age incidence has shifted*, and that for the last few

years the majority of diabetic deaths occurred in elderly people. The number of diabetic deaths in young people has very materially decreased. Now, since true diabetes is comparatively rare in elderly people, while simple glycosuria is exceedingly common, it is but reasonable to suppose that the majority of persons returned as having died from diabetes really suffered from simple glycosuria. Since this type of glycosuria does not as a rule produce coma, it is more likely that the majority of these deaths were caused by *some condition other than diabetes*. The fact that glycosuria happened to be present resulted in a return of " diabetes " being given as the cause of death. No doubt the recent introduction of insulin has tended to focus attention on glycosuria, and so its presence is more frequently determined. Glycosuria, when present, is such a definite symptom that naturally it would nearly always be mentioned under the term " diabetes " in the official certificate of death.

Again, it is certain that insulin is often not nearly so effective in the treatment of coma in the elderly as it is in the young. Coma is exceedingly detrimental to the heart, and since the heart muscle in old people frequently suffers from some degree of degeneration, it is not unusual for the patient to recover from coma and to die of cardiac failure.

All these facts may play a part in explaining the anomalous official figures which apparently suggest that insulin has failed to reduce the diabetic death-rate. These considerations indicate the marked importance of differentiating between cases of true diabetes and those of simple glycosuria of the elderly.

Insulin in Reproduction and Pregnancy.

The value of insulin in influencing reproduction in the diabetic female is well known. It was the common experience in the days before insulin that menstruation sooner or later disappeared. Even when this function

persisted pregnancy was exceedingly rare, and when it did occur the strain on the mother was so great that it seldom ended satisfactorily. Nowadays it is fairly common to meet with diabetic patients on insulin treatment who become pregnant and bear children without any undue strain or detriment to their condition. The average diabetic patient who becomes pregnant runs no greater risk than does the average normal woman, provided she is carefully treated on modern lines.

Insulin in Malnutrition.

In some non-diabetic cases of malnutrition insulin is often exceedingly useful, and the writer has seen several patients whose general condition was much benefited by small doses of insulin administered with glucose. The most suitable type of patient for this treatment is one in whom marked wasting is taking place without any very definite cause. In such a patient insulin will often work wonders.

Mode of Action of Insulin.

The manner in which insulin acts is still a matter for conjecture, and various papers are constantly appearing dealing with this aspect of the subject. Müller* made the observation that when insulin is injected into the skin it produces a more marked effect in lowering blood-sugar than when an equal amount is introduced subcutaneously. From this he argues that insulin acts, to a large extent, through nerve stimulation conducted parasympathetically, and that the marked effect of insulin when injected into the skin is dependent on the close relationship of the skin with the autonomic nervous system. These claims, though interesting, require further investigation.

An important research on the manner of insulin action has been carried out by Dale† and his co-workers, who

* *Münch. Med. Woch.*, October, 1925, p. 1677.
† *Proc. Roy. Soc.*, Communicated April 29, 1926.

showed that in the decerebrated eviscerated animal the administration of insulin results in the disappearance of sugar from the circulating fluid, and that this decrease of sugar is proportional to the increase of glycogen plus the amount of sugar destroyed by oxidation. While it must be admitted that these experiments were carried out on animals under conditions far removed from the normal, yet the results are very helpful as far as they go. Whatever insulin does, it is certain that its effects, when injected into the diabetic subject, are similar to those produced in the normal organism by its own insulin. Until we know what happens in the healthy subject we shall never know exactly what insulin does in the diabetic individual.

It is very interesting to note that the totally depancreatised dog cannot be kept alive indefinitely by insulin, though, naturally, life can be much prolonged. In the absence of *all* pancreatic tissue, death takes place after a few months in spite of insulin administration, while, on the other hand, if a small portion of the pancreas persists, life can be prolonged apparently for considerable periods. The reason for this is not yet clear, and many of the explanations advanced are not very convincing. It is not improbable that the pancreas secretes another hormone besides insulin, and that this hormone is necessary for normal carbohydrate metabolism. If this proves to be the case, it may obviously have some bearing on human diabetes.

CHAPTER X

COMA, KETONURIA, AND GLYCOSURIA

THANKS to insulin, the outlook in a case of diabetic coma is now entirely different from what it was in former days. Before the advent of insulin it might be taken as a maxim that, once coma was definitely established, the end was at hand, and no treatment was likely to prove of any avail. Now, with the help of insulin, we expect patients suffering from coma to recover, and experience shows that recovery is the general rule when the necessary treatment is intelligently applied. Coma, however, is a grave condition under all circumstances, and it is our duty to anticipate, by all means in our power, the onset of this serious complication, for early treatment of a simple nature, with attention to the diet and bowels, may often ward off a threatened attack. It may be taken for granted that coma will not come on when the urine is free from sugar and no marked ketosis is present. It is always a difficult problem to decide as to the minimum number of tests which will give the general practitioner the necessary knowledge of what is happening in a case of diabetes. Fehling's or some similar test for glucose should always be employed; the ordinary Fehling's test is quite satisfactory. As regards ketonuria, it may generally be accepted that the condition is not very grave unless the ferric chloride test in the urine is strongly positive. When this test gives a marked reaction, recourse should be had to some of the other simpler processes for investigating acidosis. Frequently, of course, the clinical condition will suggest the necessity for action, but even when the clinical condition seems to indicate marked acidosis, the use of tests may show that the acidosis is, after all, only slight.

Estimation of the free ammonia and the "ammonia coefficient" can be carried out by any medical man in about fifteen minutes, and this should be done. Investigation of the alveolar air for carbon dioxide tension by means of the Fridericia apparatus is also very easy, and frequently gives most valuable information. Sellard's sodium bicarbonate test is the simplest of all, and is often of much value.

As the minimum number of tests necessary for the treatment of bad cases of diabetes the following may be given:

1. Fehling's test for glucose (p. 75).
2. Diacetic acid test with ferric chloride (p. 94).
3. Estimation of ammonia by formalin method (pp. 96, 97).
4. Sellard's sodium bicarbonate test (p. 111).

The last two tests would only be used in the case of patients showing a well-marked reaction with ferric chloride, and in whom marked acidosis with a tendency to coma was suspected. Naturally, the more tests done the better, since no single test or combination of two or more tests is always satisfactory. The results of several tests taken in conjunction with the clinical condition will, in practically every case, enable us to obtain reliable information as to the probability of coma supervening.

Treatment of Coma.

The treatment of coma has undergone a complete change, and we now place our reliance entirely on the use of insulin. Insulin should be given in all cases, as it is the only remedy that is of any real value in this condition. It is, of course, necessary to carry out certain other measures on the lines of our old treatment, but these are only of value in so far as they assist the insulin to produce the desired effect. While there is unanimous agreement as to the wonderful effect of insulin in the treatment of diabetic coma, all authorities are, unfortunately, not quite in agreement as to certain details of this treatment. The

great danger nowadays in dealing with a case of coma is that the heart may collapse and the patient die of cardiac failure in spite of insulin treatment. Indeed, it is sometimes possible to relieve the coma condition to such an extent that the patient is apparently well, and yet death from cardiac failure may ensue. The important point, therefore, is to begin the treatment at the earliest possible moment; if this is done, and insulin intelligently administered, the patient should, as a rule, recover. The first thing to do, therefore, when called to a case of coma, is to administer insulin hypodermically or perhaps intravenously. Generally it is given hypodermically, but in a severe condition of coma intravenous injection of the first dose might be advantageous, owing to its more rapid action when administered in this way. The amount of insulin to be given must of course depend on the gravity of the condition and on the general response to treatment. As a rule, if the patient has not been taking insulin before, it is well to start with 30 units. *If at all possible, the blood-sugar should be estimated, for there is no condition in which a knowledge of the blood-sugar concentration is so useful as in the treatment of coma with insulin.* Different patients react so differently to given amounts of insulin that there is always a possible danger that an overdose may result in the patient developing symptoms of hypoglycæmia; if this condition is not recognised, but is still thought to be diabetic coma, an extra dose of insulin may prove fatal. It is, therefore, extremely important that the insulin treatment should be guided by blood-sugar estimations, for, when this is done, no untoward accident of the kind mentioned is likely to happen. While the importance of blood-sugar estimation in such cases cannot be too strongly emphasised, it may happen that the medical man may be confronted with a patient in coma under circumstances where blood-sugar control is impossible. It is then necessary to watch the urine very carefully, for as long as the patient has glycosuria, further doses of insulin may be safely given. When, for lack of facilities, the

effect of insulin on the blood-sugar cannot be ascertained, it is *most important to watch the patient as closely as possible*, and if he shows definite signs of recovery, followed by an apparent relapse, it is best to look upon the latter manifestation as a possible insulin hypoglycæmia, and to give some sugar. If the sugar does not relieve the symptoms, it may be then assumed that the condition is still one of diabetic coma, and more insulin may be given. As to how much insulin may be administered altogether, it is necessary to be guided by the symptoms, but, in the average case, 60 to 80 units or more may, as a rule, be given in the course of a few hours with safety. By very careful watching of the patient it ought to be possible to ascertain the effect of the treatment, and to be fairly certain what the condition at any particular time represents. Thus, before a patient has hypoglycæmic symptoms as the result of an excessive amount of insulin, he will pass through a stage in which he is very much better. If, after a good deal of insulin has been given, a patient appears to have practically recovered, and very soon afterwards becomes worse, it is very likely that he has passed from the condition of diabetic coma to that of insulin hypoglycæmia. Careful observation of these points will help the practitioner to treat a patient intelligently, but it must be admitted that the problem of treating diabetic coma successfully without the help of blood-sugar estimations may be extremely difficult and by no means devoid of danger. However, since the condition, if untreated, will inevitably result in death, certain risks may justifiably be taken. With facilities for blood-sugar estimation at hand, it is only necessary to estimate the blood-sugar at short intervals of half an hour or so; as long as the blood-sugar concentration remains high, more insulin may be given. When the value sinks to the region of 0·15 per cent. or so, it is not advisable to give more insulin, as a rule, unless a subsequent estimation shows that the blood-sugar is rising. If this happens, another dose may be cautiously given.

It is most important to control the condition as quickly as possible, for the danger of cardiac failure is often very great in these cases, and if this proceeds to any marked extent, death will probably ensue in spite of the administration of insulin. Hence the extreme importance of treating such patients at an early stage and in an energetic manner. If the patient has been taking a course of insulin previously, and has passed into coma in spite of the fact that he was having insulin, larger doses may be used, and as much as 50 units may be injected at once. It is quite unnecessary to give sugar during the insulin treatment of diabetic coma if the necessary facilities for carrying out blood-sugar estimations are at hand. If it is impossible to estimate the blood-sugar it is best to give some sugar by mouth as indicated later on. (See general rules, No. 1a.)

Frequently it is necessary to administer cardiac stimulants. The best drugs to employ in threatened cardiac failure are digitalin, strychnine, camphor, and alcohol.

After the first injection of insulin the patient is carefully watched, and if the symptoms do not improve within half an hour to one hour, another 20 or 30 units should be given. The chief points to note are the general mental condition, the rate and strength of the pulse, and the depth and rate of the respirations. If the pulse begins to get slower and stronger and the respirations are less deep, this indicates that improvement is setting in. Generally, if indeed not always, a second injection of insulin will be required, and at any rate is not likely to do harm. If after this there is no decided improvement, another injection of 20 or 30 units should be given in an hour or so, more especially if sugar estimations show that the blood-sugar is still remaining high.

In severe cases it may be necessary to give much more than a total of 60 to 80 units altogether, but each case must be treated on its merits. Since death is inevitable unless the symptoms can be fairly quickly controlled, it may be necessary to give somewhat heroic doses in some cases. As a general rule, it may be stated that if the administra-

tion of 40 to 60 units of insulin given within the first two or three hours produces little or no effect, then larger doses must be given, and probably another 30 units or so should be injected. It may be necessary to give still another dose one to two hours later, or even sooner than this, if the symptoms are still severe. With blood-sugar estimations it is easy enough to control the dosage, but in the absence of this, no hard-and-fast rules can be given, and each medical man must proceed as best he can on the lines indicated. If the patient is very carefully watched, there is little doubt that the risk of death from too little insulin is greater than the risk from the administration of an excessive amount, *but the latter possibility must never be forgotten.* The following general rules for the treatment of a case of coma may prove helpful:

1. Inject immediately 20 to 30 units of insulin.* Get a blood-sugar estimation done if possible. If symptoms do not improve within an hour, give another 20 units. If in 1 to 1½ hours after the second injection the symptoms are still grave, give another 20 units. If after another hour or so symptoms still remain grave, give 20 to 30 units more; if the condition still remains serious, give a further 20 to 30 units after an hour or two. Be guided by blood-sugar estimations and by the general condition, pulse-rate, and respirations. When the blood-sugar reaches the neighbourhood of 0·15 per cent. or so more insulin is generally unnecessary, and the patient must be very carefully watched for hypoglycæmic manifestations; if these appear, give 2 ounces or more of sugar in solution by mouth, or, if the patient is unconscious, intravenous injection may be necessary. For other treatment of hypoglycæmia see p. 157.

1*a*. If no facilities for blood-sugar estimations are available proceed as above and watch the patient most carefully for any improvement in the symptoms. Whenever any improvement takes place as indicated by the points just discussed, or by a return to consciousness or semiconsciousness, give 2 to 3 ounces of

* If condition is severe, give 40 units to begin with. If symptoms are not severe, 20 units may be sufficient.

sugar in solution succeeded by a dose of 20 units of insulin. If the patient continues to improve no more insulin may be necessary, but if the symptoms persist it is advisable to repeat the sugar, and to give another 20 to 30 units of insulin. The administration of sugar will prevent any hypoglycæmic symptoms, but will not materially interfere with the action of the insulin in promoting recovery. The administration of sugar with the insulin is the only safe method, when for any reason blood-sugar estimations cannot be carried out. The presence of glycosuria will also sometimes furnish a clue, but it often happens that urine is not obtainable.

2. Keep the patient quietly in bed, and see that he is warm and as comfortable as possible.

3. Get the bowels thoroughly evacuated by means of enemata and purgatives. A turpentine enema is often useful, and if ordinary aperients fail, a few drops of croton oil may be administered. If the stomach is full of food or distended, it should be emptied by means of a stomach pump.

4. Give large amounts of fluid in order to wash out the toxic products; 40 to 60 ounces may be given in 4 to 6 hours to begin with, and then rather smaller amounts. Warm liquids such as tea, coffee, clear broths, and water are best. If necessary, give liquid by rectum, or by intravenous or subcutaneous injection. Stimulants such as hot coffee and alcohol per rectum may be necessary.

5. If cardiac failure threatens, give digitalin ($\frac{1}{100}$ grain) by intravenous injection. Along with this strychnine hydrochloride ($\frac{1}{60}$ grain) or camphor (1 grain) may be given hypodermically. Camphor every two hours alternating with strychnine every two hours—*i.e.*, camphor or strychnine every hour—will be found a good combination. Alcohol may also be used if thought necessary.

6. It is not advisable to give intravenous injections of sodium bicarbonate in severe cases, for this procedure frequently appears only to accelerate the fatal issue. Sodium bicarbonate may, however, be given in small doses by mouth if desired.

7. Do not give any food until the condition has improved.

8. When the patient recovers, keep him on a low diet for a few days, giving him the amount of insulin that is found necessary. Experience shows that 10 to 20 units twice daily is a generally sufficient dose, but more may be required.

That very large doses of insulin may sometimes be necessary is shown by the following case of diabetic coma: The patient, a man aged 36, had been treated for severe diabetes a few months previously, and put on a special diet, insulin (15 units twice daily) being also given. He attended hospital at intervals for a few weeks after his dose of insulin had been worked out, and then obtained a post as commissionaire at a restaurant. He was always somewhat difficult to control as regards diet, and after a short time ceased to attend hospital. His local doctor increased his dose of insulin to 20 units twice daily, and while on this comparatively large dose no attention was apparently paid to diet, the patient eating as much as he felt inclined to take. He continued on this régime for three months, and was apparently feeling fit. Two days before admission to hospital he felt somewhat unwell, and complained of pain in his legs and chest. This was followed by some shortness of breath and general lassitude. He was then admitted to hospital in a state of coma, and treated on the lines indicated below. As will be seen from the figures given, his response to ordinary doses of insulin, as indicated by blood-sugar changes, was very slight, and large doses had to be given. Altogether, in 24 hours, he received 215 units of insulin. This case is interesting as showing the necessity for careful dieting even when comparatively large doses of insulin are being taken, For at least two months before coma, the patient had 40 units of insulin each day until his admission to hospital, and yet he developed exceedingly severe coma. Particulars of blood-sugar estimations and the general treatment adopted are tabulated on pp. 203 and 204.

The Use of Alkalies in Diabetes.

There is at the present time some diversity of opinion as to the value of alkalies in diabetic acidosis, and such an experienced authority as Joslin takes the view that they are useless and even harmful. Theoretically it is difficult to understand why they should be of value—at any rate, when given in very large amounts—since the normal mechanism for the neutralisation of acid is by means of ammonia, and plenty of ammonia is practically always available. From some experiments carried out in my laboratory by Dr. Goldblatt, it would appear that the use of alkali, at any rate in large doses, is definitely contra-indicated in diabetic coma. Goldblatt induced a ketosis in himself by starving for 48 hours. At this stage the urine contained fairly large amounts of acetone and diacetic acid, as indicated by Rothera's reaction and the ferric chloride test. This ketosis rapidly disappeared after taking some glucose. Careful observation showed that after the ingestion of 50 grams of glucose dissolved in water the ketosis disappeared entirely in almost exactly one hour. When, in addition to the glucose, a large dose of sodium bicarbonate was also taken, the ketosis persisted for a long time, and was still present in definite amounts after 8 hours. Many experiments of a similar kind were carried out, both on man and on animals; the results were always the same, and tended to show quite conclusively that sodium bicarbonate administered in the course of an acidosis markedly prolonged the condition. In the light of these experiments there can be little doubt that the ingestion of large doses of alkali during diabetic coma tends to hinder the disappearance of the coma. There can be no harm in giving small amounts, but that sodium bicarbonate is generally quite unnecessary is proved by the fact that recovery from coma takes place without the use of any alkali. It might be argued that sodium bicarbonate would be helpful in restoring the depleted alkali reserve, but there are many fallacies in such an argument.

Our present position appears to be that small doses of alkali may be advisable in diabetic coma, but that large doses are definitely harmful.

Mouth Preparations of Pancreas.

The market is at present flooded with pancreatic preparations which are alleged to be useful in the treatment of diabetes when taken by mouth. In my experience all these preparations are without effect on diabetes. I have had a thorough investigation of this point carried out in my clinic, but no evidence whatever could be obtained that any mouth preparation of pancreas had the slightest effect, either beneficial or otherwise.

Synthalin.

The latest mouth preparation is a synthetic product called "synthalin." There can be no doubt that this substance when taken by the mouth does produce a definite effect in certain cases of diabetes. The glycosuria is lessened and the ketosis is often markedly reduced. The product, however, has marked toxic properties, and tends to produce gastro-intestinal and other disturbances, so that its use in the treatment of diabetes is at present not practical. It is conceivable that some preparation of a somewhat similar constitution may be found which will have a similar action without the toxic effects of synthalin. Meanwhile we must accept the view that, for the present, the only useful substance in the treatment of diabetes is insulin.

Case of C. S., suffering from Diabetic Coma.

Time.	*Insulin Given.*	*Blood-Sugar per Cent.*	*Remarks.*
8.15 a.m.	**40 units**	0·344	Patient admitted with good pulse, 85. Air hunger very marked. Respirations 32. Not quite unconscious, but exceedingly drowsy. He attempted to answer questions, but was more or less incoherent. Strong smell of acetone. Bowels had not moved for four days. Complained of pain over right lower chest, and pressed with his hands in this region. Pain also in legs. **Large amounts of beef tea, water, coffee, and tea ordered, of which patient drank very freely.**
8.50 a.m.	—	0·362	Patient no better.
10.15 a.m.	**40 units**	—	Patient worse. Pulse 120 and weak.
10 30 a.m.	—	0·273	Much worse, very drowsy, breathing more deeply. Pulse 150, weak and thready. Heart showing signs of weakness. Mental condition also worse. **Enema given without result. Injection of camphor, gr. 1, two-hourly.**
11.30 a.m.	—	0·318	Patient worse. Pulse 150, much weaker and thready. Heart obviously getting much weaker and cardiac failure threatened.
11.45 a.m.	—	—	**Hot aperient given.**
12 noon	**40 units**	—	—
12.30 p.m.	—	0·273	Cardiac condition very bad. Heart getting very weak, with almost imperceptible pulse, 150. **Digitalin, gr. 1/100, given intravenously.**
1.15 p.m.	—	0·278	Heart slightly stronger. Pulse 130. Patient still semi-comatose.

Time.	*Insulin Given.*	*Blood-Sugar per Cent.*	*Remarks.*
1.30 p.m.	**40 units**	—	Heart still bad. Pulse 130, weak, and somewhat thready.
2 p.m.	—	—	Patient seemed a little better, but heart condition still gave cause for anxiety. Pulse 130. **Injection of gr. 1/50 strychnine hydrochloride, repeated two-hourly to alternate with camphor injection.**
2.15 p.m.	—	0·282	**Gave 3 minims croton oil.**
2.30 p.m.	—	—	**Gave turpentine enema with good result.**
3.45 p.m.	—	0·204	Patient somewhat better and less drowsy. Pulse 128, and much stronger.
4.30 p.m.	—	0·189	—
4.35 p.m.	**30 units**	—	—
5 p.m.	—	0·184	Much better. Pulse 128, fairly good. Breathing less deep and pain in chest gone. Patient vomited.
5.30 p.m.	—	0·189	Patient vomited.
6 p.m.	—	0·149	Patient very much better. Quite conscious and able to talk intelligently. Pulse good, and general condition satisfactory. Bowels open.
6.30 p.m.	—	0·119	Gave 6 ounces milk, with 1 egg and 10 grams glucose.
7 p.m.	—	0·159	Condition good.
7.30 p.m.	—	0·159	—
8 p.m.	—	0·198	—
9 p.m.	—	0·159	—
10.30 p.m.	—	0·133	—
12 p.m.	—	0·166	Condition good. Pulse 116, full and strong.
5 a.m.	—	0·254	Condition good. Pulse 104, very good. Respirations 24.
8.15 a.m.	**25 units**	—	Patient quite recovered. Pulse 95. Respirations 22.

Total insulin given in twenty-four hours = **215 units.**

APPENDIX

FOOD VALUE TABLES

THESE tables indicate the weight in grams of protein, fat, and carbohydrates contained in 1 ounce of each of the following articles of food; also the approximate caloric value of 1 ounce of the food. In each case the food should be weighed before being cooked. With a few exceptions, the composition values are calculated from the tables of Atwater and Bryant, as published in Lusk's "Science of Nutrition." In calculating calories, protein and carbohydrate are taken as being equivalent to 4 calories per gram, and fat as 9 calories per gram.

TABLE XIII.

FOODS CONSISTING CHIEFLY OF CARBOHYDRATE.

Kind of Food.		*Carbohydrate.*	*Protein.*	*Fat.*	*Calories.*
Apples, dried	1 ounce =	17	0·25	0·75	75
Apples, fresh	,, =	4	—	—	16
Apricots, dried	,, =	16	1	0·25	70
Apricots, fresh	,, =	3	0·25	—	13
Apricots, tinned	,, =	4	0·25	—	17
Asparagus, fresh	,, =	1	0·25	—	5
Bananas	,, =	6	0·25	—	25
Barley, pearled	,, =	21	2	0·25	95
Beans, dried	,, =	17	4	0·5	89
Beets, fresh	,, =	3	0·25	—	13
Bread, white	,, =	15	2	0·25	70
Bread, brown	,, =	13	1·25	0·25	60
Cabbage	,, =	1·5	0·25	—	7
Calf's foot jelly	,, =	5	0·25	—	21
Carrots	,, =	3	0·25	—	13
Cauliflower	,, =	1·5	0·25	—	7
Celery	,, =	1	0·25	—	5

FOODS CONSISTING CHIEFLY OF CARBOHYDRATE—*Continued.*

Kind of Food.			*Carbo-hydrate.*	*Protein.*	*Fat.*	*Calories.*
Cherries	1 ounce	=	4	0·25	0·25	20
Chestnuts.. ..	,,	=	11	1·5	1·5	62
Cornflour	,,	=	22	1·75	0·25	98
Cucumbers ..	,,	=	0·75	—	—	4
Dates, dried ..	,,	=	20	0·5	0·75	88
Figs	,,	=	19	1	—	80
Grapes	,,	=	5	0·25	0·25	23
Lemons	,,	=	2	0·25	0·25	11
Lentils	,,	=	17	7	0·25	100
Lettuce	,,	=	0·75	0·25	—	4
Macaroni	,,	=	21	3	0·25	98
Milk, whole ..	,,	=	1·25	1	1	19
Milk, condensed, sweet	,,	=	15	2	2	86
Oatmeal or rolled oats	,,	=	18	4	2	106
Onions	,,	=	3	0·25	—	13
Oranges	,,	=	3	0·25	—	13
Parsnips	,,	=	4	0·25	—	17
Peaches, fresh ..	,,	=	2	—	—	8
Peaches, tinned ..	,,	=	3	—	—	12
Pears, fresh ..	,,	=	4	—	—	16
Pears, tinned ..	,,	=	5	—	—	20
Peas, green ..	,,	=	5	1·5	—	26
Peas, tinned ..	,,	=	3	0·75	—	15
Plums	,,	=	5	0·25	—	21
Potatoes, raw ..	,,	=	5	0·5	—	22
Prunes, dried ..	,,	=	20	0·5	—	82
Pumpkins ..	,,	=	1·5	0·25	—	7
Radishes	,,	=	1·5	0·25	—	7
Raspberries ..	,,	=	3	0·25	0·25	16
Rhubarb	,,	=	1	—	0·25	6
Rice	,,	=	22	2	—	96
Snaps (ginger) ..	,,	=	21	1·5	2	108
Spinach	,,	=	1	0·5	—	6
Strawberries ..	,,	=	2	0·25	—	9
Tapioca	,,	=	25	—	—	100
Tomatoes ..	,,	=	1	0·25	—	5
Turnips	,,	=	2	0·25	—	9
Wheatflour, whole meal	,,	=	20	3	0·5	96
Wheatflour, white	,,	=	21	2	0·25	94

Foods consisting Chiefly of Protein.

Kind of Food.		*Carbo-hydrate.*	*Protein.*	*Fat.*	*Calories.*
Beef, rump, corned	1 ounce =	—	4	6	70
Beef juice	,, =	—	1	—	4
Beef, loin, lean	,, =	—	5	3	47
Beef, loin, fat	,, =	—	5	7	83
Beef, tongue	,, =	—	5	2	38
Cheese, Cheddar	,, =	1	7	9	113
Cheese, Brie	,, =	—	4	6	70
Cheese, cream	,, =	1	7	9	113
Cheese, Roquefort	,, =	—	6	8	96
Chicken	,, =	—	6	1	33
Cod steak	,, =	—	5	—	20
Eggs	,, =	—	4	3	43
Flounder	,, =	—	4	—	16
Fowl	,, =	—	5	4	56
Haddock, fresh	,, =	—	5	—	20
Halibut, steak	,, =	—	5	1	29
Ham, fresh	,, =	—	4	8	88
Ham, smoked	,, =	—	4	10	106
Herring, fresh	,, =	—	6	2	42
Herring, smoked	,, =	—	10	4	76
Lamb, leg	,, =	—	5	4	56
Lamb, neck	,, =	—	5	7	83
Lamb, shoulder	,, =	—	5	9	101
Mutton, leg	,, =	—	5	5	65
Mutton, neck	,, =	—	5	7	83
Mutton, shoulder	,, =	—	5	5	65
Mutton, tongue, tinned	,, =	—	6	6	78
Mackerel, fresh	,, =	—	5	2	38
Sardines, tinned	,, =	—	5	5	65
Salmon, tinned	,, =	—	3	3	39
Sausage, Bologna	,, =	—	5	5	65
Trout, fresh	,, =	—	5	3	47
Turkey	,, =	—	6	6	78
Veal cutlets	,, =	—	6	2	42

FOODS CONSISTING CHIEFLY OF FAT.

Kind of Food.		*Carbo-hydrate.*	*Protein.*	*Fat.*	*Calories.*
Almonds ..	.. 1 ounce =	4	5	14	162
Bacon ..	.. „ =	—	3	18	174
Brazil nuts	.. „ =	2	5	19	200
Butter ..	.. „ =	—	—	23	207
Butter nuts	.. „ =	1	7	16	176
Cream ..	.. „ =	1	0·5	5	51
Hickory nuts	.. „ =	3	4	17	181
Lard ..	.. „ =	—	—	27	243
Margarine	.. „ =	—	—	22	198
Olive oil ..	.. „ =	—	—	28	252
Peanuts ..	.. „ =	6	6	10	138
Pork chop, loin	.. „ =	—	4	8	88
Sausages, pork	.. „ =	—	4	12	124
Walnuts ..	.. „ =	4	5	18	198

NOTE ON SPECIAL DIABETIC PREPARATIONS.

Various trade preparations are advertised as suitable for diabetic patients. These products are generally claimed to be free from carbohydrate, and in this respect some of them fulfil all the claims that are made on their behalf. On the other hand, some of the so-called "starch-free" preparations sometimes contain large amounts of starch, or perhaps starch may be substituted by dextrin, so that the claim of freedom from starch may be literally true though practically quite false. It is by no means uncommon for so-called diabetic breads to contain more carbohydrate than is present in ordinary white bread. Certain firms, however, issue quite reliable products. In London Messrs. Callard specialise in diabetic preparations, and their goods seem to be satisfactory. Recently Messrs. Allen and Hanbury have introduced a special carbohydrate-free flour which is useful in certain cases of diabetes. I have tested some of the products made from

this flour according to the instructions of the makers, and found them very satisfactory as to taste and freedom from carbohydrate.

In general it must be stated that no special preparations are necessary in the great majority of diabetic cases. The various protein flour products are very concentrated, so that a comparatively large amount of protein is taken in small bulk, and generally this is inadvisable in diabetes. In special circumstances, however, some of these preparations are very useful, and serve a purpose in the milder types of the disease.

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